Familial risk for anxiety and depression: intergenerational effects and genetic transmission

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Familial risk for anxiety and depression: intergenerational effects and genetic transmission

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Abstract

Symptoms of anxiety and depression are common and debilitating emotional problems, experienced by both adults and children. Described collectively as 'internalising' problems, they share much of the same genetic aetiology and typically co-occur in individuals. Robust evidence exists for the clustering of internalising problems in families, as symptoms in parents are associated with symptoms in offspring. Many questions remain as to the pathways underpinning such familial risk. Parent-offspring associations could reflect causal pathways, whereby parents' symptoms directly influence child symptoms, and vice versa. However, associations could be non-causal if the same genes influence symptoms in both parents and offspring. Understanding these processes can help to shed light on the pathways that shape our mental health and ultimately help to refine intervention targets to prevent the development of psychiatric problems.

In this thesis I use genetically informative research designs to approximate and control for genetic effects in intergenerational associations involving parent and offspring internalising symptoms. Results help us to understand whether it is ever reasonable to draw causal inferences about the influence of parent and offspring internalising symptoms on one another. I present five studies to contribute both clinically relevant and methodological lessons. Specifically, I seek to explore the possibility of transactional effects or co-development between parent and offspring symptoms across time; seek ways to improve generalisability of findings by including data from a wider pool of participants; and attend to questions surrounding statistical power to detect genetic effects in families.

In my first study I conduct a meta-analysis to show that concurrent associations between parent anxiety and offspring internalising problems withstand correction for genetic confounding, while associations involving prenatal exposure to maternal anxiety do not. In my second study I use data from a longitudinal adoption cohort to show prospective prediction from child anxiety symptoms to mother anxiety symptoms during middle childhood; and prospective prediction from father anxiety symptoms to child anxiety symptoms. In my third study I show that associations between parental criticism and adolescent internalising problems withstand correction for genetic confounding, using an extended Children-of-Twins design. I present power analyses for the detection of genetic confounding using this design and explore the possible direction of causation between generations. In my fourth study I introduce a novel approach to combining developmental methods with a statistically powerful Multiple-Children-of-Twins/Siblings model. I show that mothers' internalising symptoms do not co-develop with offspring temperament during early childhood, although baseline stability in mothers' symptoms is associated with baseline stability in offspring emotionality, via both genetic and non-genetic pathways. In the final chapter I discuss the findings and limitations of these approaches, alongside possible avenues for future research.

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Statement of authorship

All work presented in this thesis is my own, except where acknowledged in the text. All investigations were carried out by me, as first author, in collaboration with colleagues included in the author lists at the start of each chapter. Chapter-specific author contributions are described below. Data collection for the samples used in Chapters 3, 4 and 5 were completed by the respective research teams prior to my involvement. I co-ordinated and conducted data collection for Chapter 6, with the help of the research team acknowledged below.

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Chapter 2:

Y.A conceived and designed the investigation with support from T.M, J.B-P and C.C; Y.A and M.H conducted the systematic literature search; Y.A carried out statistical analyses with support from T.S; Y.A wrote and revised the manuscript; all co-authors critically reviewed the manuscript.

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1. Background

Familial similarity is evident for many forms of psychopathology. In the context of anxiety and depression, which are described collectively as internalising problems, researchers find robust evidence for intergenerational associations. That is, symptoms in parents are predictive of symptoms in offspring (Connell & Goodman, 2002; Goodman et al., 2011; Kane & Garber, 2004; Kim, Capaldi, Pears, Kerr, & Owen, 2009; Lawrence, Murayama, & Creswell, 2018; Micco et al., 2009; Sydsjo, Agnafors, Bladh, & Josefsson, 2018; Weissman et al., 2016). Understanding the pathways that underpin parent-offspring internalising associations is necessary for the development of efficacious interventions to tackle the transmission of symptoms in families. There are a number of possible explanations for intergenerational associations involving internalising symptoms, none of which are mutually exclusive. First, children may inherit genes associated with the development of internalising problems from their parents. Second, parents experiencing internalising symptoms may behave in ways, both pre- and postnatally, that directly influence the development of child internalising. Third, children experiencing internalising symptoms may behave in ways that directly influence the development of parents' internalising symptoms. Fourth, environments shared across a family may jointly influence the development of both parent and child internalising. To better understand intergenerational associations involving parent and child internalising problems, researchers must strive to test for all of these pathways. Doing so requires the use of genetically informed research designs.

In this thesis I present a series of studies designed to advance our knowledge of the social and genetic pathways that underpin familial risk for internalising symptoms. Collectively, the presented studies expand on existing designs in quantitative genetics to: (1) look across time, examining temporal change and transactional associations between generations; (2) improve generalisability of findings, looking beyond mother-child dyads in twin and adoption samples; and (3) address statistical power issues to identify genetic transmission effects on parent-offspring associations. In this first chapter I provide a brief overview of what is known about internalising symptoms in parents and offspring. I then provide an introduction to genetically informative research designs and findings to date. To end, I outline the three main challenges addressed in this thesis for advancing research efforts and provide a summary of the thesis aims and structure.

1.1. An introduction to internalising problems

1.1.1. Defining internalising symptoms and disorders

Internalising symptoms encapsulate emotional problems that are characteristic of anxiety and/or depression. Core emotional symptoms include worry, fear, sadness and withdrawal. Associated difficulties also include low self-esteem, poor concentration, tiredness and somatic complaints (Achenbach & Edelbrock, 1983; APA, 2013; WHO, 2004). It is when these symptoms occur more

often than usual, last for prolonged periods of time, become severe, and substantially disrupt aspects of daily life that they warrant a professional, psychiatric diagnosis. For clinical diagnostic purposes, internalising symptoms can be partitioned into disorder-specific presentations, representing the extreme, debilitating ends of quantitatively normal symptom distributions (Krueger & Eaton, 2015; Krueger & Piasecki, 2002). The most common internalising disorders include major depression, social anxiety disorder, generalised anxiety disorder and phobias. However, internalising symptoms are highly comorbid and pervasive across diagnostic groups, with around half of patients with a depressive disorder also being diagnosed with an anxiety disorder (Kessler et al., 1996; Kroenke, Spitzer, Williams, Monahan, & Löwe, 2007). Moderate tetrachoric correlations are observed between anxiety and depressive disorders (Kessler, Berglund, Demler, Jin, & Walters, 2005). In factor analyses of all psychiatric conditions, internalising symptoms cluster within one higher order factor (Caspi et al., 2014; Kessler et al., 2011). These disorders also show significant overlap in genetic aetiology (Krueger & Markon, 2006; Waszczuk, Zavos, Gregory, & Eley, 2014). As such, the 'internalising' umbrella term is used throughout this thesis, as elsewhere, to describe the array of interconnected, highly prevalent, emotional symptoms (Krueger & Eaton, 2015).

1.1.2. Prevalence estimates and societal impact

Internalising problems constitute the most common forms of psychiatric impairment worldwide (Baxter, Scott, Vos, & Whiteford, 2013; Kessler et al., 2009; Remes, Brayne, van der Linde, & Lafortune, 2016; Wittchen et al., 2011). Each year in the EU, it is estimated that 14% (60 million people) of the population are affected by anxiety disorders and 7% (30 million people) by depressive disorders, with extensive overlap in those affected by both (Wittchen et al., 2011). In the USA, large-scale surveys of adults and adolescents show that 22% of individuals experience an anxiety disorder annually and 7% major depressive disorder (Kessler, Petukhova, Sampson, Zaslavsky, & Wittchen, 2012). In turn, internalising disorders are ranked among the most burdensome of all diseases, involving impairment of cognition, mobility, self-care, social interaction, life activities and participation (Hendriks et al., 2014; Ravindran, Matheson, Griffiths, Merali, & Anisman, 2002). Together, these consequences place significant strain on healthcare and other social-welfare systems (Lepine, 2002; Richmond-Rakerd et al., 2020; WHO, 2017; Wittchen et al., 2011). Individuals experiencing symptom levels that do not reach diagnostic criteria remain unaccounted for in disorder-level statistics, although their symptoms also exert significant morbidity and strain on national services, compared to unaffected individuals (Goldney, Fisher, Dal Grande, & Taylor, 2004; Haller, Cramer, Lauche, Gass, & Dobos, 2014; Roberts, Fisher, Turner, & Tang, 2015).

1.1.3. Age of onset and developmental perspective

The average age of onset for anxiety occurs during childhood, and depression during early adulthood (Kessler et al., 2007). Among European populations, emotional disorders affect

approximately 8% of 5- to 19-year olds annually, as the most common form of mental disorder in this age group (Sadler et al., 2018), and there are widespread concerns that prevalence is increasing (Durbeej et al., 2019). In a large New Zealand-based cohort, data suggests that around half of individuals who experience a psychiatric disorder in their lifetime will experience their first onset before age 18 years (Caspi et al., 2020). This is supported by work showing that internalising symptoms are prevalent during adolescence and predictive of diagnoses during adulthood (Roberts et al., 2015; Shankman et al., 2009). After the onset of symptoms, depression can be episodic, long-lasting or recurrent; while anxiety disorders typically take a chronic course (WHO, 2017). Overall, variance shared across internalising disorders appears to serve as the primary pathway for disorder persistence over time, with very few individuals keeping and maintaining only a single diagnosis (Caspi et al., 2020; Krueger & Eaton, 2015). While debilitating, internalising symptoms do not appear to impact fecundity in adulthood (C. D. Lynch, Sundaram, Louis, Lum, & Pyper, 2012). This means that the prevalence among parents should be about equal to that among non-parents, leaving vast numbers of children exposed to internalising symptoms in the family.

1.2. Familial risk: parent-child associations

1.2.1. Epidemiological findings

Children raised by parents experiencing internalising symptoms are at increased risk for developing similar problems of their own (Connell & Goodman, 2002; Kim et al., 2009). Meta-analytic findings show that anxiety disorders among parents confers significant risk for anxiety disorders *and* depression among offspring, irrespective of the parent's particular type of anxiety (Lawrence et al., 2018; Micco et al., 2009). Intergenerational transmission of anxiety disorders and depression can be observed across three generations, with child risk highest among those with both an affected parent *and* grandparent (Pettit, Olino, Roberts, Seeley, & Lewinsohn, 2008; Sydsjo et al., 2018; Weissman et al., 2016). Parent depression is predictive of many forms of offspring maladjustment, including internalising disorders (Goodman et al., 2011; Kane & Garber, 2004). In one longitudinal study of 262 parents with recurrent depression, authors found high rates of mental health problems among offspring, including 45% with elevated depression symptoms (Collishaw et al., 2016). Only 20% sustained good mental health through adolescence. Epidemiological findings in a large UK cohort suggest that while parent depression symptoms are phenotypically associated with a wide range of child adjustment problems, parent anxiety may show more specific associations with child internalising problems (E. D. Barker, Jaffee, Uher, & Maughan, 2011).

1.2.2. The direction of intergenerational effects

While parent-offspring associations are typically interpreted as indicating parental impact on offspring, it is also possible for effects to operate in the opposite direction. Longitudinal research shows that child internalising symptoms can prospectively predict parents' internalising

symptoms, as well as parent symptoms prospectively predicting child symptoms (Elgar, Curtis, McGrath, Waschbusch, & Stewart, 2003; Fanti, Panayiotou, & Fanti, 2013; Villarreal & Nelson, 2018). In support of these findings, evidence from experimental and intervention-based research shows that manipulation of symptom severity in offspring can predict change in parents' symptoms, and vice-versa. In one meta-analysis of randomised controlled trial (RCT) data, authors showed positive effects of parental psychotherapy on offspring mental health and parenting interactions, although the need for more high-quality research was emphasised (Cuijpers, Weitz, Karyotaki, Garber, & Andersson, 2015). Similarly, authors of another review showed that five out of nine studies examining psychopathology among offspring whose parents received treatment for depression found improvements in child psychopathology, including anxiety and depression (Gunlicks & Weissman, 2008). Results from a feasibility RCT suggest that parenting skills training in the context of high parental anxiety could ameliorate risk for anxiety among offspring (Cartwright-Hatton et al., 2018). Other RCTs have shown effects in the reverse direction, with treatment of child anxiety being associated with a reduction in parent anxiety (Creswell et al., 2020; Lavallee, Schuck, Blatter-Meunier, & Schneider, 2019).

1.2.3. Considering the role of parenting

Parenting behaviours have been particularly targeted in research exploring family-based processes that may underpin parent-child internalising associations. Internalising symptoms in both mothers and fathers may be associated with compromised caregiving capabilities. For example, parents experiencing symptoms of depression have been shown to engage in less healthy feeding and sleep practices with their offspring and display lower levels of sensitivity and higher negative affect with offspring (Field, 2010; Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Paulson, Dauber, & Leiferman, 2006; Wilson & Durbin, 2010). Parents experiencing symptoms of anxiety may be overprotective of offspring and/or have a tendency to overcontrol their child's environment (Aktar, Nikolić, & Bögels, 2017). It is suggested that anxious parents may display higher levels of parenting difficulties during times of stress in particular, compared to depressed parents who may show more pervasive difficulties (Murray et al., 2012). Review papers and meta-analytic results suggest that parenting difficulties are associated with offspring internalising problems, although they explain only a modest proportion of the total variance. For example, more punishment and lower levels of autonomy granting, monitoring and reassurance from parents are associated with child depression and related internalising problems; while high levels of parental control are linked to child anxiety (McLeod, Wood, & Weisz, 2007; van der Bruggen, Stams, & Bogels, 2008; van der Sluis, van Steensel, & Bogels, 2015; Wood, McLeod, Sigman, Hwang, & Chu, 2003; Yap, Pilkington, Ryan, & Jorm, 2014). Longitudinal research again shows a role for transactional effects, whereby parenting behaviours exert influence on the child and child behaviours exert influence on the parenting that they receive (Barbot, Crossman, Hunter, Grigorenko, & Luthar, 2014; Kok et al., 2013; Nelemans, Hale Iii, Branje, Hawk, & Meeus, 2014). Although most parenting interventions have been focussed on addressing child behaviour (i.e.,

externalising) problems, some evidence suggests that changes in parenting behaviours can reduce emotional symptoms of anxiety and depression in offspring (Cartwright-Hatton, McNally, White, & Verduyn, 2005; Cuijpers et al., 2015).

It is clear from existing, correlational research that internalising problems in parents are predictive of internalising problems in offspring. Further, longitudinal and experimental research suggests that these associations may arise from social interactions in the family environment, as parents and offspring are exposed to symptoms of psychopathology in one and other. However, parents and offspring share more than just an environment, they also share their DNA. To better understand the causal pathways underpinning parent-child internalising associations, and to identify where may be best to focus treatment and prevention strategies, it is important for researchers and clinicians to understand the role of genetic relatedness in families.

1.3. Genetic relatedness in the family context

1.3.1. Genetic transmission

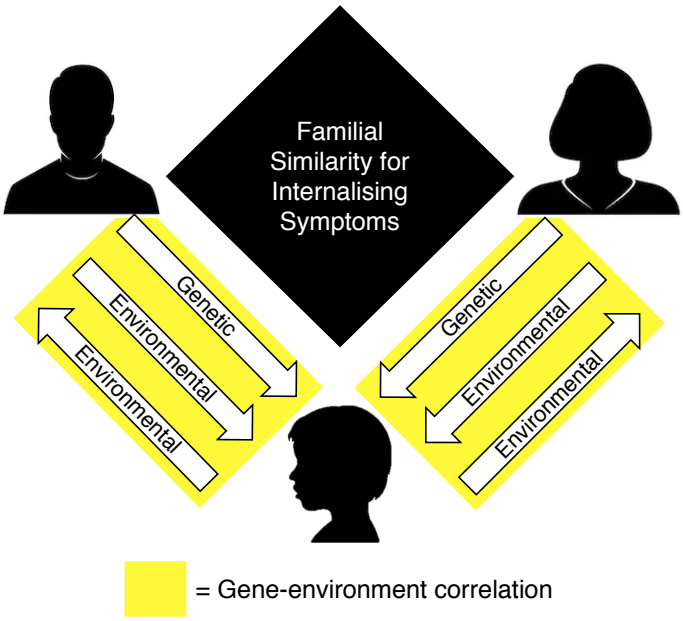
Genetic factors influence all human behaviours and experiences to some degree (Kendler & Eaves, 1986; Plomin, DeFries, Knopik, & Neiderhiser, 2016; Polderman et al., 2015). Trait heritability describes the proportion of population variance in any trait that is attributable to genetic factors. Trait heritability has traditionally been derived from twin studies, where estimates for internalising problems tend to fall between 25 – 50% (Hettema, Neale, & Kendler, 2001; Sullivan, Neale, & Kendler, 2000). Results are similar, although more heterogeneous, in child populations (Franic, Middeldorp, Dolan, Ligthart, & Boomsma, 2010; Rice & Thapar, 2009), with some evidence for increasing heritability of internalising problems during adolescence (Garcia et al., 2013; Rice & Thapar, 2009; Scourfield et al., 2003). Others have found that heritability estimates decrease during adulthood, owing to an increase in environmental variance, although longitudinal stability is mostly attributable to genetic factors among both adults and children (Hannigan, Walaker, Waszczuk, McAdams, & Eley, 2016; Nivard et al., 2015b). Further, longitudinal research shows evidence for innovation and attenuation of genetic factors influencing internalising problems from childhood through adolescence, highlighting change in genetic influence across development (Kendler, Gardner, Annas, et al., 2008; Kendler, Gardner, & Lichtenstein, 2008; Nivard et al., 2015a; Waszczuk et al., 2014).

Environmental influence on any trait is estimated in twin research alongside trait heritability. This includes estimating the influence of environments that are shared between twins and make twins more similar to one another. Shared environments incorporate any influence from parents that is shared between twins in family (Klahr & Burt, 2014). That is, if a parent's behaviour jointly influences the development any trait among twin offspring, this will be captured under influence of their shared environment on that trait. Although traditional twin studies go some way toward explaining how internalising problems can run in families, through quantifying the influence of genes and shared environments on offspring development, they ultimately miss part of the picture.

It is also important to understand the factors underlying correlations *between* generations. Less is known about the role of genetic factors that influence parent-child internalising associations in families, which make parents and offspring more similar to one another. It is possible that parents who experience genetically influenced symptoms of internalising can pass on some genes associated with the development of internalising to their offspring. As a result, any effect of genetic transmission on internalising problems in families may confound estimation of the causal, environmentally mediated effects of parent and child symptoms on one another (see Figure 1). This is known as gene-environment correlation, of which there are two forms that are relevant to within-family transmission: passive and evocative (Horwitz & Neiderhiser, 2011).

Figure 1. Genetic and environmental pathways are at play in families to influence parent-child similarity for internalising symptoms

Pathways (shown in arrows) are correlated with one another. Genetically informed research designs are required to tease apart their relative influence.



1.3.2. Passive gene-environment correlation

Passive gene-environment correlation occurs in biological families where parents provide both genetic and environmental influences on the child. As such, the environment shared by parents and offspring is 'passively' correlated with the genes that they share (Horwitz & Neiderhiser, 2011). This makes it difficult to distinguish potential causal effects between generations from effects that are attributable to relatedness. For example, previous research shows that the concurrent association between maternal depressive symptoms and offspring perceived self-competence is partially due to (and thus confounded by) genetic effects (Class et al., 2012). In

other words, the same genes that are associated with the mother's depression symptoms are transmitted to the child at conception, where they exert influence on the child's perceived self-competence during adolescence. Genetically informed research designs are needed to identify the influence of genetic transmission, which acts as a common cause, or confounder, in associations between the parent and child traits. Evidence for genetic confounding contradicts assumptions of causality between the parent and child traits. If the parent and child traits do not exert causal influence on one another then treatment of the parent or child trait will not work to reduce symptoms in the other. This is important to know, given that interventions to alleviate mental health risk in families might be targeted differently if intergenerational transmission appears more linked to genetic transmission rather than the family environment.

1.3.3. Evocative gene-environment correlation

Evocative gene-environment correlation provides another route by which the family environment can become associated with genetically influenced behaviours (Horwitz & Neiderhiser, 2011). Evocative gene-environment correlation denotes that individuals can 'evoke' changes in their environment that are correlated with their genome. For example, previous research shows that high child anxiety can evoke changes in maternal control, with both phenotypes under influence from the child's genes (Eley, Napolitano, Lau, & Gregory, 2010). In other words, genes in the child generation can exert influence on behaviours in *both* generations, thereby confounding estimations of any causal influence of the parent's behaviour on the child. The reverse effects are also relevant, if parents' genetically influenced behaviours evoke changes to the parent's environment via influence on the child's behaviour. This would occur as a result of parent-to-child effects, rather than confounding estimates of the parent's influence on the child. Overall, the actions and experiences of each family member, and in turn their family environment, become shaped in some way by their genetic makeup (Kendler & Baker, 2007; Plomin, DeFries, & Knopik, 2012; Scarr & McCartney, 1983). Again, genetically informative research designs are needed to investigate the presence of evocative gene-environment correlation, to better ascertain the influence and direction of causal pathways between generations.

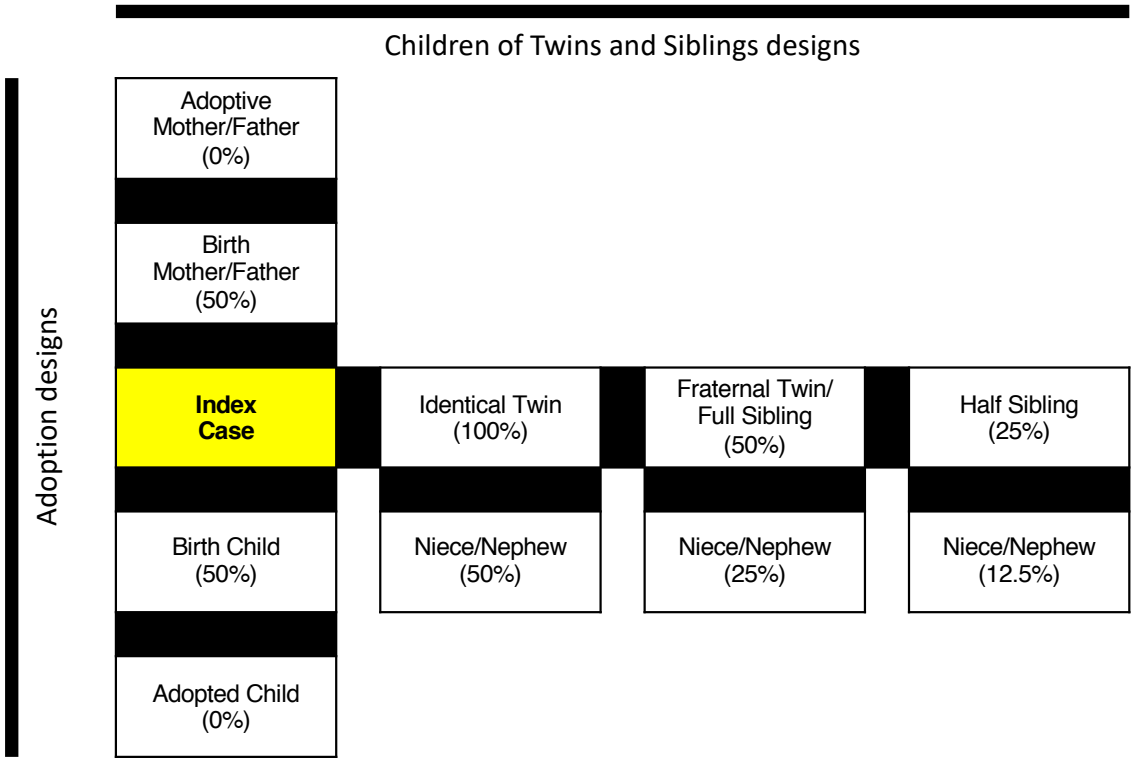
1.4. Genetically informed research designs

A number of genetically informed research designs have been developed to facilitate causal inference in parent-child associations. These designs cannot prove causality between two variables, but can show whether parent and child traits do or do not continue to predict one another after controlling for shared genetic aetiology (D'Onofrio, Lahey, Turkheimer, & Lichtenstein, 2013; Plomin et al., 2012). By estimating the influence of genetic effects across generations, genetically informative designs allow environmental sources of variation to be distinguished from those that are genetically confounded (Neiderhiser, 2001). These designs rely on the principal that if genetic factors affect a behaviour of interest, then phenotypic resemblance of relatives should increase with increasing degrees of genetic relatedness (Fisher, 1918). As

shown in Figure 2, the degree of genetic relatedness between family members can be approximated given that each individual inherits 50% of their genetic material from each of their birth parents. Working outwards from the index case in Figure 2, the genetic relatedness between different family members and the index case is reduced. Three key natural experiments, based on the logic depicted in Figure 2, are used and/or discussed in this thesis to examine parent-child associations: (1) Adoption designs, (2) Children-of-Twins/Siblings designs, and (3) Sibling Comparison designs.

Figure 2: The key feature of quantitative genetics designs: approximation of genetic relatedness between relatives

Potential relatives of the index case are shown. Brackets show the degree of genetic relatedness between each relative and the index case (adapted from figure on p35 in Plomin et al., 2012).



1.4.1. Adoption designs

When children are adopted at birth, they share their genes and prenatal rearing environments with their birth parents, but not their postnatal rearing environment. As such, intergenerational associations between children adopted at birth and their birth parents are indicative of shared genetic effects and/or prenatal exposure effects, but not exposure effects from the postnatal

rearing environment. Children adopted at birth share their postnatal rearing environment with their adoptive parents. Intergenerational associations between children adopted at birth and their adoptive parents are therefore indicative of effects in the postnatal rearing environment, not shared genetic or prenatal effects. Adoptive families provide a means to control for passive gene-environment correlation in the study of postnatal rearing environments, because there is no genetic transmission between the adoptive parents and their adopted child (Figure 2). Evocative effects are identified when genetically influenced behaviours in adopted children predict adoptive parents' behaviour. The logic of adoption designs can be extended to children conceived via gamete or embryo donation, who are essentially 'adopted at conception' and not genetically related to their rearing parents (Thapar et al., 2007). Offspring conceived via in vitro fertilisation (IVF), inherit their genes from their biological parents but share their pre- *and* postnatal rearing environments with their 'adoptive' parents. As such, IVF designs build on traditional adoption designs by providing a means to control for passive gene-environment correlation in the study of *prenatal* rearing environments. Here, the role of the prenatal environment is not influenced by the effects of genetic transmission between the 'adoptive' parent and their 'adopted' child. Again, evocative effects are identified if the child's genetically influenced behaviours (including during foetal development) predict the 'adoptive' parents' behaviour.

1.4.2. Extended family designs: Children-of-Twins/Siblings

Identical twins share 100% of their genes. Fraternal twins and full siblings share on average 50% of the genetic variants that differ within human populations, and half-siblings 25% (Figure 2). Therefore, in extended families linked by different types of adult siblings, aunts and uncles are genetically related to their nieces and nephews by varied degrees. For example, in the families of identical twin pairs, the offspring of one twin is just as genetically related to their own parent as they are to their parent's identical twin (50% with both). However, in the families of full or half-siblings, the offspring of one sibling is more genetically related to their own parent (50%) compared to their parent's full or half-sibling (25% or 12.5% respectively). In extended family designs, it is assumed that children share their immediate rearing environment with their own parent, not their parent's sibling (i.e., their aunt/uncle). This means that phenotypic correlations between children and their aunts/uncles (also known as 'avuncular' associations) can be used to estimate the effect of genetic relatedness on intergenerational associations. If avuncular associations are stronger in families who are more genetically related, this indicates a role of shared genetic effects acting across generations. Researchers can statistically account for the role of genetic relatedness on intergenerational associations using structural equation modelling, to estimate the potential influence of social pathways in the rearing environment, above and beyond what is attributable to genetic transmission. Statistical power for this approach is strongest in families where the parent generation comprises twin pairs, who have high levels of genetic sharing. As such, most research involving extended family designs has used Children-of-Twins (CoT) designs, without involvement of other sibling types (McAdams et al., 2014).

1.4.3. Sibling Comparison designs

Data on siblings who are reared together provide another opportunity for genetically informed research, using sibling comparison designs. It can be assumed that genetic transmission of risk-associated genes for psychiatric traits is equal between full-siblings at a population level, on average, given the random nature of inheritance (Plomin et al., 2016). Further, when reared together, it can be assumed that siblings are equally exposed to broad aspects of the family environment, including socio-economic and cultural factors (Petersen & Lange, 2020). This makes it possible to control for unmeasured, within-family confounding (including passive gene-environment correlation) in the context of any exposure that differs between siblings. Exposures can include measures of parental internalising symptoms. For example, siblings who do not share a pregnancy (i.e., those who are not twins) will be differentially exposed to perinatal internalising symptoms in their mother. For postnatal exposure, non-twin siblings will be differentially exposed to internalising symptoms in their parents across different stages of their development. Researchers can use the sibling comparison design to examine differences in developmental outcomes between siblings, relative to differences in their degree of exposure at any given age, while broadly eliminating unmeasured confounding by genetic and environmental factors (e.g., Gjerde et al., 2018; Gjerde et al., 2019). The direction of effects between generations is typically not examined and it must be assumed that siblings do not significantly influence one-another (Lahey & D'Onofrio, 2010).

1.4.4. Extending Children-of-Twins designs: including child twins/siblings

In traditional Children-of-Twins designs, statistical power to decompose genetic and environmental covariance between parent and child traits depends on several factors. These include the magnitude of the phenotypic parent-child correlation; proportion of the correlation attributable to genetic overlap; size of the avuncular genetic correlations; total sample size; ratio of twin/sibling types in the parent generation; heritability of the parent and offspring behaviours; and power to detect heritability within each generation (McAdams et al., 2018; Verhulst, 2017). When Children-of-Twins analyses are underpowered to detect genetic covariance, the parent-child association appears attributable to environmental covariance. This is because environmental covariance is calculated as the residual parent-offspring correlation, once the effects of genetic transmission are accounted for (Keller et al., 2009; McAdams et al., 2018). To avoid underpowered analyses, at least two extensions of the Children-of-Twins design have been developed.

1.4.4.1. Extended-Children-of-Twins (ECoT) designs

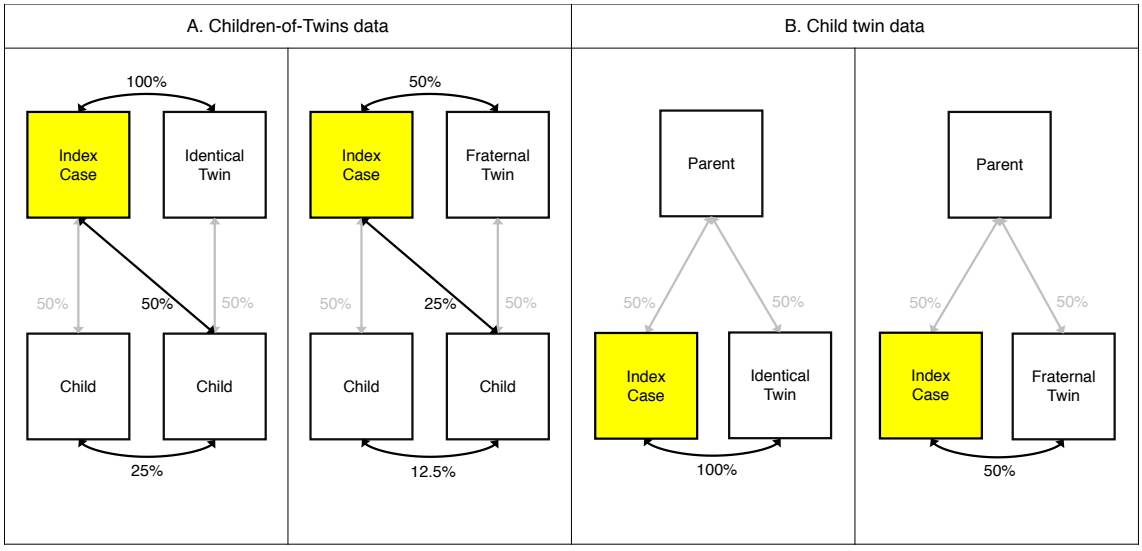
Traditional Children-of-Twins designs rely upon comparison of cousin pairs to detect child trait heritability. This can be problematic for statistical power, given that cousins have low levels of genetic sharing (25% in identical twin families, 12.5% in fraternal twin families; Figure 3A). In an ECoT design, researchers seek to boost power by combining Children-of-Twins data with child

twin data (Narusyte et al., 2008; Silberg, Maes, & Eaves, 2010). Child twin data comprises information on twin pairs who are children, typically with one parent per child twin pair (Figure 3B). Child twins show higher levels of genetic sharing compared to child cousins (100% in identical twin families, 50% in fraternal twin families; Figure 3B). Unlike cousins, child twins are reared in the same family environment. Therefore, inclusion of child twin data within a Children-of-Twins design offers three advantages. First, information on child twins can bolster heritability estimates for the child trait. Second, information on child twins can be used to estimate influence of the shared family environment on the child trait. Third, child twin data can help to generate a more precise estimate of the overall phenotypic parent-child correlation, by contributing two phenotypic estimates per child twin pair (see two parent-offspring paths per parent in Figure 3B).

Much of the work using ECoT designs to date has been conducted using Children-of-Twins data from the Twin and Offspring Study in Sweden (TOSS; Neiderhiser & Lichtenstein, 2008) and child twin data from the Swedish Twin Study of Child and Adolescent Development (TCHAD; Lichtenstein, Tuvblad, Larsson, & Carlstrom, 2007). Both samples comprise adolescent offspring, with corresponding measures used across several parent and offspring traits. When combined, these datasets yield around 4,000 parent-offspring pairs for analyses, which have been used in previous research to examine parent-child internalising associations (Hannigan, Rijsdijk, et al., 2018; Horwitz et al., 2015; Narusyte et al., 2008). Recent work highlights some misspecification of previously published ECoT models (McAdams et al., 2018), which are addressed in Chapter 4 of this thesis.

Figure 3. Extended-Children-of-Twins (ECoT) designs

Paths show genetic relatedness coefficients between family members.

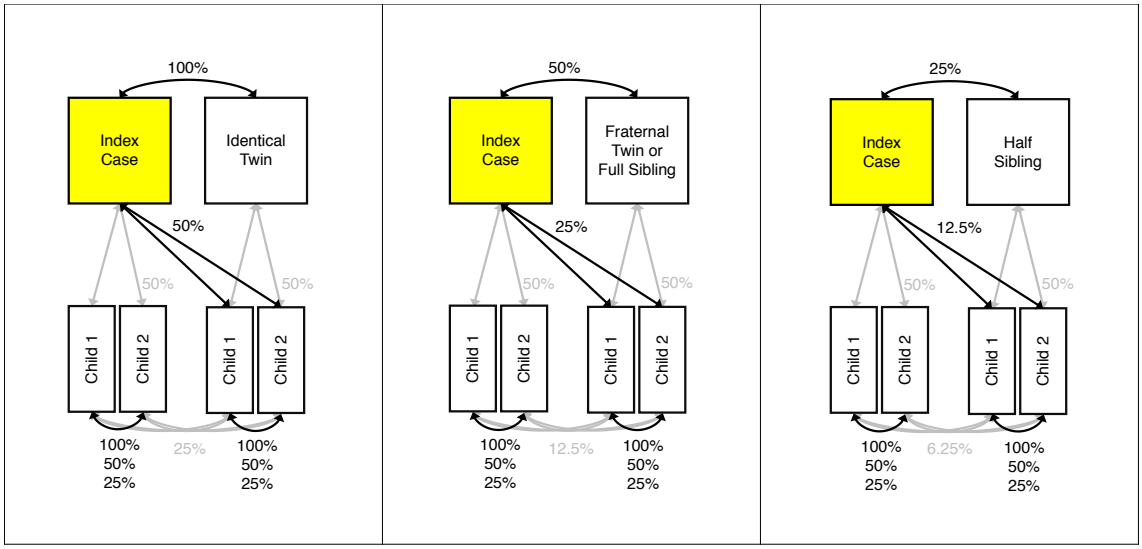


1.4.4.2. Multiple-Children-of-Twins/Siblings (MCoTS) designs

MCoTS designs provide another approach to improving statistical power in Children-of-Twins and extended family designs, by including data on multiple children per parent (McAdams et al., 2018). These children can be twins, full siblings or half siblings. As in ECoT designs, variation in genetic sharing between child siblings (ranging from 100% to 25%; see Figure 4) can be included in analyses to bolster heritability estimates of the child trait, alongside cousin comparisons. Child siblings are also used to estimate influence of the shared family environment on the child trait. As well as comparing differentially related siblings and cousins in the MCoTS design, it also becomes possible to examine differentially *exposed* siblings. This follows the same logic as in sibling comparison research, whereby non-twin siblings will be differentially exposed to variations in their parent's phenotype, across different stages of their development. In the context of the MCoTS design, sibling comparison in the child generation enables researchers to simultaneously model two unique parent-offspring *and* two unique avuncular correlations per adult twin family (see two parent-offspring paths and two avuncular paths per parent in Figure 4), which helps to greatly improve statistical power for the detection of genetic transmission effects between generations (McAdams et al., 2018).

Figure 4. Multiple-Children-of-Twins/Siblings (MCoTS) designs

Paths show genetic relatedness coefficients between family members.



MCoTS models were developed for use with data from the Norwegian Mother, Father and Child Cohort Study (MoBa; Magnus et al., 2016), although others had previously taken a similar approach using Swedish population registry data (Kuja-Halkola, D'Onofrio, Larsson, & Lichtenstein, 2014). The MoBa comprises data from approximately 95,000 mothers, 75,000

fathers and their 115,000 offspring. Many of the adults taking part in this study are related and their kinship can be identified using national registry data (namely the Norwegian Twin Registry, Medical Birth Registry of Norway, and Norwegian Population Registry; McAdams et al., 2018). Furthermore, around 16,400 mothers in the MoBa participate with more than one child. It is therefore possible to identify pairs of twins, full-siblings and half-siblings among both parents and offspring in the MoBa, to map extended families for inclusion in MCoTS models. Power simulations for the MoBa data show that inclusion of two offspring per parent in Children-of-Twins research can substantially reduce the number of families required to detect effects of intergenerational genetic transmission (McAdams et al., 2018).

1.5. A brief overview of research findings to date

1.5.1. Adoption data

Results from the Early Growth and Development Study (EGDS; Leve et al., 2019), using a prospective adoption design, suggest that associations exist between adoptive mother and child internalising symptoms, above and beyond any effects of genetic transmission or prenatal factors (Roos et al., 2016). As such, genetic transmission and prenatal factors cannot account for all familial similarity in internalising problems within this sample. These results are replicated across a much larger literature focussed specifically on symptoms of parental depression. Here, results from the EGDS adoption sample show evidence for influence of the postnatal environment in both cross-sectional and longitudinal associations between maternal depression and child internalising symptoms during early childhood (Kerr et al., 2013; Laurent et al., 2013; Natsuaki et al., 2010). The same is found in other adoption and IVF cohorts, where significant associations are reported between parent depression and offspring internalising, among unrelated parent-offspring pairs (Lewis, Rice, Harold, Collishaw, & Thapar, 2011; Rice, Lewis, Harold, & Thapar, 2013; Tully, Iacono, & McGue, 2008). The few studies published on intergenerational associations using parental anxiety symptoms show results consistent with the depression literature (Brooker et al., 2014; Brooker et al., 2011; Brooker et al., 2015; Rice et al., 2010). However, questions remain as to the contribution of fathers and child-to-parent effects. Only two studies of internalising problems within adoptive families have considered the direction of effects between generations, both showing evidence for child-to-parent effects (Brooker et al., 2015; McAdams et al., 2015). Across the few adoption studies to have examined father-child associations, results are mixed as to whether differences exist in comparison with mother-child associations (e.g., Brooker et al., 2015; Hails et al., 2019; Pemberton et al., 2010).

Adoption and IVF designs can only infer information about genetic transmission effects using phenotypic data from biological parents, as ‘proxy’ measures for offspring genetic risk. To date, findings suggest that birth parent internalising problems are more closely linked to offspring externalising problems, rather than offspring internalising (Brooker et al., 2015; Kerr et al., 2013; Marceau et al., 2013; McAdams et al., 2015; Pemberton et al., 2010; Rice et al., 2010). It could

be that the methodology used in adoption and IVF designs is not sensitive enough to detect subtle genetic effects linking parent and offspring internalising. Or, existing findings could reflect change in genetic risk architecture across development, if the genes that influence externalising problems in childhood go on to influence internalising problems during adulthood (Kendler, Gardner, Annas, et al., 2008; Kendler, Gardner, & Lichtenstein, 2008; Nivard et al., 2015a; Waszczuk et al., 2014). In other words, genetic risk associated with internalising symptoms during adulthood may be specific to these symptoms in adults, and not in children. Evidence for genetic transmission effects has been found for offspring depression problems when examining adopted offspring during adulthood, with substantial similarity reported for major depression between biological parents and their adult adopted offspring (Kendler, Ohlsson, Sundquist, & Sundquist, 2018).

1.5.2. Children-of-Twins (CoT) and Extended-Children-of-Twins (ECoT) data

Like adoption studies, published CoT and ECoT studies have been focussed on understanding associations between parental depression and child outcomes, more so than parental anxiety or broader measures of internalising symptoms. Depression results are comparable with those from the adoption literature. Findings show that environmental pathways can explain cross-sectional associations between parent depression and offspring internalising symptoms in middle childhood and adolescence (Class et al., 2012; McAdams et al., 2015; Silberg et al., 2010; Singh et al., 2011). In a 2014 systematic review of all Children-of-Twins research (McAdams et al., 2014), authors showed that genetic covariance was only reported in the context of parental depression for cross-sectional associations with offspring externalising outcomes (Silberg et al., 2010; Singh et al., 2011). Limited Children-of-Twins research has been conducted on associations involving parental anxiety. Results from one study suggest that genetic transmission could not explain parent-child anxiety associations during adolescence (Eley et al., 2015). Together, these papers suggest that the family rearing environment may be important for familial similarity in internalising (although most evidence is specific to parent depression symptoms), with evidence for genetic transmission effects only reported in the context of offspring externalising problems.

A small Children-of-Twins literature exists for the study of associations between parenting behaviours and offspring internalising, where results again suggest that phenotypic associations cannot be explained by the effects of genetic transmission (Hannigan, Rijsdijk, et al., 2018; Horwitz et al., 2015; S. K. Lynch et al., 2006; Narusyte et al., 2008; Schermerhorn et al., 2011). One study of the direction of effects between generations has been conducted for familial internalising problems, using an ECoT approach, showing that adolescent internalising problems may exert stronger effects on parent emotional overinvolvement compared to the reverse (Narusyte et al., 2008; although see Chapter 4 of this thesis for a critique of their methodology). Longitudinal data has not yet been modelled using Children-of-Twins designs, however researchers recently examined lagged associations between parent symptoms and prospective child internalising problems, using an MCoTS approach with the MoBa data, as discussed below.

1.5.3. Multiple-Children-of-Twins/Siblings (MCoTS) and Sibling Comparison data

Results from a recent MCoTS study using the MoBa data suggest that prospective associations between maternal depression (both pre- and postnatally) and offspring internalising symptoms *are* attributable to genetic transmission effects (Hannigan, Eilertsen, et al., 2018). This finding is supported by sibling comparison analyses for both maternal depression and anxiety in the MoBa, where genetic transmission effects are observed for lagged associations (again, both pre- and postnatally; Bekkhus et al., 2018; Gjerde et al., 2018; Gjerde et al., 2017). The MCoTS approach has also shown evidence for genetic transmission effects on *concurrent* associations between parent depression and offspring internalising symptoms, which has not been shown in previous Children-of-Twins research (Gjerde et al., 2019). This finding is most likely attributable to the unprecedented statistical power harnessed in the MCoTS design, as applied to the unprecedented sample size in the MoBa. Overall, MCoTS research suggests that genetic transmission effects *are* at play in parent-offspring internalising associations, but perhaps went undetected in previous adoption and Children-of-Twins research that lacked the statistical power to detect genetic effects on moderate or weak intergenerational associations.

1.5.4. Summarising where gaps lie in the existing literature

The research published to date suggests that genetic confounding cannot account for all familial similarity in internalising problems. However, significant gaps remain in our understanding. Crucially, there has been a narrow focus on the study of parent depression symptoms, with very few studies of parental anxiety. Even fewer have capitalised on the phenotypic and genetic overlap in anxiety and depression for research purposes, by studying these problems in combination using general internalising measures. Furthermore, research has been predominantly based on cross-sectional parent child associations, with minimal reference to the possibility of child-to-parent effects and change across time. Researchers have also predominantly examined mother-child dyads, rather than including data from fathers, siblings, and other members of the extended family. Finally, questions remain as to our ability to detect the true effects of genetic transmission acting on parent-offspring internalising associations, given that recent research has begun to uncover evidence for genetic effects that were previously considered absent. These points are addressed throughout this thesis and outlined in further detail below, under three key aims for this thesis.

1.6. Introducing three key aims for this thesis

1.6.1. Looking across time: temporal change and transactional associations between generations

As outlined in the previous sections, parent and child internalising problems are predictive of one another at a phenotypic level. However, gaps remain in our understanding as to how these intergenerational associations operate longitudinally. That is, to what extent do parents and

offspring influence one another's mental health *across time*, once we control for the effects of genetic confounding? Exploration of transactional effects between generations is rarely combined with genetically informative methods. Studies of adoptive families suggest that infant negative affect can prospectively predict adoptive mother and father anxiety symptoms (Brooker et al., 2015); and child internalising problems in middle childhood can prospectively predict adoptive parent depression symptoms (McAdams et al., 2015). Further, ECoT research suggests that adolescent internalising problems may predict negative parenting practises (Narusyte et al., 2008). However, these studies provide exceptions to a general limitation across the genetically informed, and indeed broader developmental, literature, where there is little mention of the possibility of child-to-parent effects. For example, in one review of genetically informative research on parent depression and offspring adjustment, the authors did not mention the possibility of child-driven or evocative effects in families (Natsuaki et al., 2014).

In this thesis, I aim to contribute new knowledge on temporal change and transactional associations between generations, in the context of familial internalising. I begin in Chapter 2 with a systematic review of all literature on associations between parent anxiety symptoms and offspring internalising. Here I confirm the scarcity of longitudinal research conducted to date, and lack of consideration for child-to-parent effects. In Chapter 3 I conduct novel research on transactional effects between mother, father and offspring anxiety symptoms. I build on existing research with adoptive families (Brooker et al., 2015; McAdams et al., 2015), to investigate parent-child anxiety associations during middle childhood. In Chapter 4, I introduce new model specification for a reciprocal causation ECoT model (Narusyte et al., 2008), to explore whether we can identify a causal direction of effects between parental criticism and offspring internalising symptoms during adolescence. I discuss the importance of considering child-to-parent effects, even within cross-sectional analyses (Heath et al., 1993). In Chapter 5, I conduct the first Children-of-Twins/Siblings study to incorporate longitudinal data points in a single model. I examine intergenerational associations between stability and change in parent and offspring internalising traits, during three years of early childhood. Sibling comparison studies using the MoBa data suggest that non-genetic influences are present only for concurrent parent-child internalising associations, not longitudinal, lagged associations (Gjerde et al., 2018; Gjerde et al., 2017). I build on this work, to explore both genetic and non-genetic influences on *co-development* of parent and offspring symptoms across time. In Chapter 6 I describe new data collection for a novel Children-of-Twins cohort, which will include data on three generations, two of which are followed from birth. This new sample promises novel opportunities for longitudinal research on temporal change and transactional associations between generations, in the context of familial risk for internalising problems.

1.6.2. Improving generalisability of genetically informed research: looking beyond mother-child dyads in twin and adoption samples

Within the literature discussed so far, analyses have been limited by a focus on mother-child dyads in highly specific family types (i.e., adoptive parents or parents who are twins). This may create problems with the generalisability of results. Data on fathers has been missing from most studies for a range of methodological and/or sociocultural reasons (e.g., relating to data collection constraints and/or mothers being more likely to take part in research than fathers; B. Barker, Iles, & Ramchandani, 2017; Parent, Forehand, Pomerantz, Peisch, & Seehuus, 2017; Phares, 1992). This is problematic given that fathers provide 50% of offspring DNA and, if involved in child rearing, embody a substantial portion of the family environment. One study of adoptive families shows the importance of examining both mother-child and father-child internalising associations together, as symptoms in one parent may have more effect on the child if symptoms are also present in the other parent (i.e., a statistical moderation effect; Hails et al., 2019). In such instances, information from only one parent would not provide the full picture. The EGDS cohort provides data from both birth and adoptive mothers and fathers, providing scope to include fathers in new research on adoptive families.

Exclusive use of adoptive parents is unavoidable for adoption designs. However, for extended family studies it is possible to move away from exclusive use of parents who are twins, who may not be representative of the general population (e.g., it has been suggested that adult identical twins have more frequent contact compared to non-identical siblings; Koenig, Jacob, Haber, & Xian, 2010). In the MoBa cohort it is possible to model data from different types of extended families, including those linked by parents who are full- or half-siblings, or even cousins. We can also include information on child siblings, to avoid randomly selecting only one child per parent. Most parents have more than one child and it is not possible for parents to have an equal relationship with each of their offspring, given the transactional nature of parent-offspring relationships (Sameroff, 2009) and offspring age differences (if the offspring are not twins). Therefore, inclusion of more than one parent-offspring relationship per family can help to build a clearer picture in research as to how intergenerational relationships function (Pike, Atzaba-Poria, & Kretschmer, 2016). Further, inclusion of multiple offspring in the Children-of-Twins design helps to estimate the aetiology of child traits without relying on exclusive use of child twin samples. In summary, there is scope within existing datasets to broaden out our target sample, moving away from modelling very niche family structures in the context of familial risk for internalising problems. I capitalise on these opportunities in the chapters of this thesis. By examining more generalisable models of family kinship I aim to produce more generalisable results.

In Chapter 3, I make use of the rich data available from the EGDS adoption cohort to concurrently examine mother-child, father-child and mother-father anxiety associations in the same models. I work towards a family systems approach using a cross-lagged panel analysis. In Chapter 4 I use an ECoT approach, merging family data from a sample of adult twins with children and a sample

of parents with child twins, to create a sample that does not exclusively include twins in either generation. In Chapter 5 I use an MCoTS approach to model data on twins, full-siblings and half-siblings in both the parent and child generations. Further, I extend the models to incorporate extended families linked by cousins in the parent generation, as well as pairs of unrelated sisters-in-law (whose children are cousins) and unrelated cousins-in-law (whose children are first cousins once removed). By modelling a wider range of family structures, bringing siblings and new types of extended families into the Children-of-Twins models, I aim to derive more generalisable results about parent-offspring relationships in families. In Chapter 6 I discuss our recruitment protocol for a new Children-of-Twins cohort, where we aim to include both adult twins *and* their spouses, along with multiple offspring per family unit. Here I discuss plans for future analyses making use of data from all family members, as and when it becomes available, in the new sample.

1.6.3. Considering statistical power to identify genetic transmission effects on parent-offspring internalising associations

Previous research shows that internalising traits are at least moderately heritable (see section 1.3.1), and that parent and child internalising problems are predictive of one another at a phenotypic level (see section 1.2.). Therefore, it is likely that genetic transmission from parents to offspring will at least partially account for familial similarity in internalising problems. However, as discussed above, data from adoption studies and Children-of-Twins designs have shown minimal evidence for genetic overlap between parent and child internalising symptoms, with more evidence for genetic overlap with offspring externalising problems (Brooker et al., 2015; Eley et al., 2015; Kerr et al., 2013; Marceau et al., 2013; McAdams et al., 2015; Pemberton et al., 2010; Rice et al., 2010; Silberg et al., 2010; Singh et al., 2011). It could be that child internalising problems are genetically unrelated to adult internalising problems, or perhaps the existing literature has been derived mostly from statistically underpowered analyses. The latter seems more likely, given that recent findings using statistically powerful MCoTS models in the MoBa (McAdams et al., 2018) *do* show novel evidence for genetic covariance between parent and child internalising problems (Gjerde et al., 2019; Gjerde et al., 2017; Hannigan, Eilertsen, et al., 2018). It is problematic that power analyses were not reported in previously published Children-of-Twins papers, making their null findings for genetic transmission effects difficult to critically interpret.

Throughout this thesis I aim to address uncertainties relating to the detection of genetic transmission effects on parent-offspring internalising associations. In Chapter 3 I investigate whether intergenerational genetic effects can be identified for internalising problems in the adoption design if a broad, lifetime measure of birth parent internalising problems, or even total psychiatric problems, is used. Authors have typically relied upon less intensive phenotyping among birth parents in previous adoption studies, which may have resulted in a poorer index of the offspring's total genetic risk (e.g., Brooker et al., 2015). In Chapter 4 I conduct novel power analyses for an ECoT design in the TOSS and TCHAD datasets, to aid interpretation of my results and those previously published (e.g., Hannigan, Rijsdijk, et al., 2018; Horwitz et al., 2015;

Narusyte et al., 2008). Finally, in Chapter 5, I use an MCoTS design with data from the MoBa to test for genetic confounding in associations between maternal internalising and offspring temperament during early child development. I harness new statistical power for these analyses, with the novel inclusion of extended families linked by cousin pairs and genetically unrelated brother/sister-in-law pairs (whose children are related to one another). I combine measures of parent anxiety and depression to capitalise on their shared genetic aetiology and phenotypic presentation, building on existing work that has been restricted to the study of parent depression symptoms only (Gjerde et al., 2019; Hannigan, Eilertsen, et al., 2018). Moving beyond work in the MoBa sample, it will be important to take similar approaches to maximising statistical power in other Children-of-Twins cohort studies, as discussed in the context of our new Children-of-Twins cohort in Chapter 6.

1.7. Summarising the aims and structure of this thesis

The aim of this thesis is to help build our understanding of the pathways that underpin familial risk for internalising problems. Ultimately, the studies presented are intended to contribute new information and methodology to refine intervention targets for families at risk of experiencing anxiety and depression. My research questions are approached in the context of the three challenges outlined above: considering transactional effects and the co-development of parent and child symptoms across time; the benefits of incorporating less niche family structures in research; and addressing questions surrounding statistical power to detect genetic transmission effects. Scope for this novel research is rich, drawing on data from existing multi-generational adoption, twin and family datasets. The following paragraphs provide an overview of each study.

Chapter 2 comprises a systematic review and meta-analysis of existing, genetically informative research examining associations between parent anxiety and offspring internalising outcomes. Only eight published studies are identified, derived from data collected across only four cohort studies. Results from adoption, IVF, Children-of-Twins and sibling comparison designs provide preliminary evidence for both genetic and environmentally mediated intergenerational associations, although information is lacking on longitudinal stability, directionality between generations and the role of moderating variables.

Chapter 3 emphasises the importance of including fathers in research, taking a two-parent perspective to the study of parent-offspring anxiety associations during middle childhood. Using a longitudinal adoption design, I provide evidence for environmentally mediated, transactional effects between generations, demonstrating that child symptoms can exert influence on caregivers.

Chapter 4 addresses statistical power in an Extended-Children-of-Twins (ECoT) design, examining the association between parental criticism and offspring internalising symptoms during adolescence. Results suggest that this parent-offspring association is not confounded by genetic

relatedness, although statistical power was not sufficient to detect small effects of shared genes. The direction of causation between generations is explored.

Chapter 5 seeks to build on statistical power issues outlined in Chapter 4, using a Multiple-Children-of-Twins/Siblings (MCoTS) design, to explore associations between maternal internalising and offspring emotionality during early childhood. Longitudinal data across three time-points are combined with the genetically informative design, introducing a novel approach to examine stability and change in parent and offspring symptoms over time.

Chapter 6 introduces a new Children-of-Twins study, developed to follow the children of twins enrolled in an existing birth cohort study. This is the first twin study to include life-long information on both parents and offspring, making it possible examine anxiety and depression phenotypes in depth across generations and lifespans.

Taken together, these studies – each using different methodologies and samples to examine different developmental periods – address important gaps in our existing understanding of familial risk for internalising problems. I highlight limitations of this work and possible future directions in the discussion of this thesis, in Chapter 7.

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2. Associations between parent anxiety and offspring internalising problems: a systematic review and meta-analysis of genetically informed research

This chapter is adapted from a manuscript that is currently undergoing the process of peer-review. Supplementary materials for this chapter, as detailed in the text, are included in Appendix A (page 170).

Ahmadzadeh, Y. I., Schoeler, T., Han, M., Pingault, J.-B., Creswell, C., McAdams, T. A. (in revision). Associations between parent anxiety and offspring internalising problems: A systematic review and meta-analysis of genetically informed research. *Journal of the American Academy of Child and Adolescent Psychiatry*.

2.1. Abstract

Background: Parent anxiety is associated with offspring internalising problems (emotional problems related to anxiety and depression). This may reflect causal processes, whereby exposure to parent anxiety directly influences offspring internalising (and/or vice versa). However, genetic relatedness in families may lead to non-causal associations if the same genes influence parent and offspring symptoms. We present a systematic review and meta-analysis to investigate whether parent anxiety is associated with offspring internalising problems after controlling for genetic relatedness.

Method: A literature search in five databases identified 429 records. Publications were retained if they used a genetically informed design in a general population sample to examine associations between parent anxiety and offspring internalising problems. Studies of pre- and postnatal anxiety exposure were meta-analysed separately. Pearson's correlation coefficient estimates (*r*) were pooled using multilevel random effects models.

Results: Eight publications were retained. Data were drawn from four population cohorts ($N_{families}$=12,990), each unique to a genetically informed design: adoption, sibling-comparison, children-of-twins or in vitro fertilisation. Across three publications, no association was found between *prenatal* anxiety exposure and offspring internalising problems during childhood, after accounting for shared genetic risk (*r*=.04, CI -.07,.14). Across six publications, a small but significant association was found between *concurrent* symptoms in parents and offspring during childhood, after accounting for shared genetic risk (*r*=.13, CI .04,.21).

Conclusions: A sparse, genetically informed literature suggests that prenatal exposure to anxiety does not cause offspring internalising outcomes via non-genetic pathways. However, postnatal anxiety exposure may be causally associated with concurrent offspring internalising. Longitudinal stability and the role of moderators and methodological biases require attention.

2.2. Introduction

Anxiety disorders are the most prevalent class of mental disorders worldwide (Kessler et al., 2009). They are characterised by pervasive emotional and physical distress that can substantially restrict daily functioning (Mendlowicz & Stein, 2000). The median age of onset for anxiety disorders is 11 years (Kessler, Berglund, Demler, Jin, & Walters, 2005). Anxiety symptoms and disorder diagnoses cluster within families, with disorder status among parents being a robust predictor of related internalising problems among developing offspring (Lawrence, Murayama, & Creswell, 2018; Micco et al., 2009; Sydsjo, Agnafors, Bladh, & Josefsson, 2018). Internalising problems encapsulate emotional symptoms characteristic of both anxiety and depression. Core internalising symptoms include worry, fear, sadness, and withdrawal (Achenbach & Edelbrock, 1983). Parent anxiety could pose an environmental risk for the development of offspring internalising problems, for example via modelling processes and social learning (Aktar, Nikolić, & Bögels, 2017; Ginsburg & Schlossberg, 2002; Lieb et al., 2000; Wood, McLeod, Sigman, Hwang, & Chu, 2003), or via foetal programming during pregnancy (Aktar, Qu, et al., 2019; Glover, 2014; Lautarescu, Craig, & Glover, 2020; O'Connor, Monk, & Fitelson, 2014). It is also possible that child symptoms influence parents' symptoms, resulting in environmentally mediated transactional effects between parents and offspring (Elgar, Curtis, McGrath, Waschbusch, & Stewart, 2003; Fanti, Panayiotou, & Fanti, 2013; Hudson, Comer, & Kendall, 2008; Villarreal & Nelson, 2018). However, genetic transmission from parents to offspring is likely to at least partially account for symptom associations across generations. It is important to distinguish the potential effects of familial exposure from associations attributable to genetic relatedness, to inform the development of successful intervention and prevention strategies.

Previous research on associations between parent anxiety and offspring internalising outcomes has mostly relied upon observational studies, where researchers may adjust for measured confounding but cannot account for unobserved variables, including genetic factors (e.g., Aktar, Van Bockstaele, Perez-Edgar, Wiers, & Bogels, 2019; Bögels & Brechman-Toussaint, 2006; Polte et al., 2019; Rees, Channon, & Waters, 2019; van der Bruggen, Stams, & Bogels, 2008). This is a major limitation that can lead to ambiguous results, where causal associations are indistinguishable from those attributable to common causes. Population variance in anxiety and related internalising problems is attributable in part to genetic influences (Hettema, Neale, & Kendler, 2001; Hettema, Prescott, & Kendler, 2004; Sullivan, Neale, & Kendler, 2000), with the same genetic factors found to influence multiple internalising phenotypes across the lifespan (Hannigan, Walaker, Waszczuk, McAdams, & Eley, 2016; Kendler et al., 2011; Waszczuk, Zavos, Gregory, & Eley, 2014). It is therefore reasonable to expect that genetic factors influencing anxiety in adult parents may also act in their genetically related offspring, manifesting as similar problems during childhood. Further, genetic transmission in families becomes correlated with aspects of the family environment, as genetically influenced behaviours in each generation exert influence on the other (Knafo & Jaffee, 2013). For example, children's heritable internalising behaviours

can evoke changes in their parents' behaviour via environmental pathways (Avinun & Knafo, 2014). Additional evidence for this phenomenon is provided by longitudinal studies that highlight dynamic, transactional processes between family members across time (Elgar et al., 2003; Fanti et al., 2013; Villarreal & Nelson, 2018). In sum, evidence from genetic and longitudinal research shows that purely observational studies cannot provide robust conclusions as to whether and how parent anxiety might directly influence the development of child internalising problems. It is important to first control for confounding by shared genes, then ask questions about the direction of effects between generations.

2.2.1. Experimental research

To explore the causal pathways linking parent anxiety and offspring internalising problems, researchers can use either experimental or quasi-experimental methods. Experimental methods are used in medical research to test the effect of an exposure (or intervention) on an outcome, with randomised controlled trials (RCTs) typically labelled the 'gold standard'. It is unfeasible and unethical to experimentally randomise children to be reared by anxious versus non-anxious parents. Instead, researchers can temporarily exacerbate anxiety in parents or offspring, using controlled experiments, to examine whether increases in symptoms in one generation predict the same in the other. For example, parents' fear responses to a novel toy can predict offspring fear and avoidance behaviours (Gerull & Rapee, 2002). Another experimental approach involves researchers treating parent or offspring symptoms and examining whether symptom improvements in one generation predict improvements in the other. RCT data shows that treatment of child anxiety is associated with a reduction in parent anxiety (Creswell et al., 2020; Lavallee, Schuck, Blatter-Meunier, & Schneider, 2019). Treatment of parental anxiety may also help to improve child outcomes, in combination with child-focussed treatment (Cobham, Dadds, Spence, & McDermott, 2010), although evidence is not always consistent (Creswell & Cartwright-Hatton, 2007; Hudson et al., 2014). In sum, experimental research studies provide some evidence for causal effects between parent anxiety and offspring internalising symptoms, but they cannot inform on the nature of the association outside of the experimental setting, nor on the influence of genetic transmission in naturalistic settings. In the context of epidemiological research, experiments are limited because they tell us how things *can be*, rather than how they *are* in a population.

Quasi-experiments provide an alternative approach to experimental trials, that can be used to test the possibility that causal mechanisms underlie associations between an exposure and an outcome. Within a quasi-experiment, the exposure of interest (e.g., parent anxiety) is naturally occurring and not manipulated by the investigator. Unique design features are used to account for unmeasured variables that are confounded with the hypothesised causal environment, such as genetic relatedness between parents and offspring, to strengthen causal inferences (Barnighausen et al., 2017; Pingault et al., 2018; Shadish, Cook, & Campbell, 2002). A range of genetically informed quasi-experimental research designs have been developed for this purpose,

comparing family members for whom genetic relatedness is known or can be approximated (D'Onofrio, Lahey, Turkheimer, & Lichtenstein, 2013; Plomin, DeFries, & Knopik, 2012). Family types integral to these designs include: parents with adopted children; parents with children conceived via gamete or embryo donation; identical and nonidentical twin pairs with children; and parents with two or more children who are differentially exposed to the variable of interest. These designs help to tease apart the role of genetic and environmental transmission effects across generations. When combined with longitudinal data, they can shed light on the direction of effects between generations.

2.2.2. Genetically informed quasi-experiments

2.2.2.1. Adoption and in vitro fertilisation (IVF) designs

When used for quasi-experimental purposes, adoption designs require data from parents and offspring adopted at birth (Leve et al., 2019; Plomin & Defries, 1983). In such studies, similarities between *birth* parents and the adopted child reflect only genetic and prenatal influences, because postnatal contact is absent. Similarities between *adoptive* parents and their adopted child are free from confounding by genetic relatedness, so are used to examine influence of the rearing environment on child development, independent of genetic effects. The IVF (or 'cross-fostering') design follows a similar premise for offspring conceived via gamete or embryo donation, who are essentially 'adopted at conception'. Where embryos are implanted into unrelated mothers, the IVF design can be used to distinguish the influence of both pre- *and* postnatal rearing environments from genetic effects (Thapar et al., 2007). Longitudinal data using both 'adoption at birth' and 'adoption at conception' study designs allows for examination of environmentally mediated effects between generations (e.g., Ahmadzadeh et al., 2019; Brooker et al., 2015). A major advantage of adoption designs is that they eliminate any effect of shared genes in associations between parents and offspring *by design*, because they use genetically unrelated parent-offspring dyads. However, a caveat to this is that participants in adoption and IVF studies may not be representative of the general population, so results may not be generalisable and sample sizes are usually small.

2.2.2.2. Children-of-twins designs

Children-of-twins designs require data on identical (monozygotic, MZ) and fraternal (dizygotic, DZ) adult twin pairs with children (D'Onofrio et al., 2003; Heath, Kendler, Eaves, & Markell, 1985; McAdams et al., 2014). In MZ twin families, offspring are just as genetically related to their parent's identical twin, who is their aunt or uncle, as they are to their own parent (genetic correlation=.50 with both individuals). In DZ twin families, offspring are less genetically related to their aunt/uncle (genetic correlation=.25 on average) as compared to their own parent (genetic correlation=.50). As such, if offspring are more similar to their aunt/uncle for any given trait in MZ compared to DZ families, an effect of shared genes is indicated. Following this logic, researchers statistically estimate and control for the role of shared genes between parent and offspring generations.

Residual parent-offspring associations are unconfounded by genetic relatedness and comprise the environmental effect of parents on offspring, and vice versa, as well as any unmeasured confounding (i.e., additional confounding that is not captured by controlling for shared genetic influences). Extensions of the design can include more than one child per parent and different combinations of adult siblings, including half siblings and unrelated siblings-in-law (Khemiri et al., 2020; McAdams et al., 2018; Torvik et al., 2020). It is also possible to model the influence of environments shared across all members of nuclear/extended families. Analyses are reliant upon an 'equal environments assumption', positing that the children of MZ twins are not exposed to their parent's twin any more so than the children of DZ twins (which has been found to hold true in previous research; Koenig, Jacob, Haber, & Xian, 2010). Children-of-twins data have not yet been modelled longitudinally in research.

2.2.2.3. Sibling-comparison designs

Sibling-comparison designs are unique in that they do not rely upon differentially related individuals, but instead on siblings who are differentially exposed to a given environment. Specifically, sibling-comparison designs require a sample of parents with at least two children, where sibling differences exist for the independent variable/exposure (e.g., prenatal maternal anxiety; Petersen & Lange, 2020). Siblings are naturally matched into family units where they broadly share many potential confounding variables, including their parents, home and family environment, and genetic factors (genetic correlation between siblings=.50 on average). Researchers compare groups of differentially exposed, family-matched siblings on an outcome of interest (e.g., internalising problems), to examine the exposure effect whilst eliminating within-family confounding. It can be assumed that genetic risk transmission is equal between siblings at a population level, on average, given the random nature of inheritance. As such, researchers simultaneously control for both unmeasured genetic *and* environmental confounding. Typically, no distinction is drawn between parent-to-child and child-to-parent effects and it must be assumed that siblings do not significantly influence one-another (Lahey & D'Onofrio, 2010).

2.2.3. Additional sources of confounding

The discussed quasi-experimental designs account for genetic confounding in different ways and require specific sub-populations of families on whom phenotypic data has been collected. These designs cannot control for all potential confounds and each design is characterised by a set of methodological caveats and assumptions. Shared method variance can arise when parents report on both their own and their offspring's symptoms, thereby inflating estimates of intergenerational associations in research. The length of time elapsed between measurement of the exposure (parent anxiety) and outcome (child internalising) can also influence results, with concurrent associations typically being stronger than those with a lagged outcome (e.g., Gjerde et al., 2018; Gjerde et al., 2019). Results may also differ depending on child age or developmental period, participant sex, socio-economic status, presence of comorbid diagnoses, or reliability of the

measures used for data collection. As such, it is important that researchers consider both measured and unmeasured confounders, whilst drawing on a range of quasi-experimental research designs and protocols, to yield reliable and robust conclusions (Rutter & Quinton, 1984).

2.2.4. Aims

We conduct the first systematic literature review to identify all existing empirical research where authors have accounted for familial genetic confounding in associations between parent anxiety and offspring internalising outcomes. We focus on quasi-experimental research. We exclude studies that involve experimental manipulation of anxiety state within families and observational research where controls are not included for unobserved sources of confounding. Results relating to prenatal and postnatal parent anxiety exposure are investigated separately, as they relate to distinct forms of anxiety exposure, with distinct hypothesised modes of transmission (Aktar, Qu, et al., 2019). We provide a narrative synthesis, critique, and meta-analysis of the retrieved literature. Our primary aims were to examine the following questions:

a) Is parent anxiety associated with offspring internalising outcomes after accounting for familial genetic confounders?
b) If so, what can we tell about the direction of effects between parents and offspring?
c) If extracted data permits further analysis of moderator terms, to what extent is the magnitude of the parent-child association affected by methodological (e.g., study design, reporter, time-lag between exposure and outcome) and/or observed (e.g., sex, age, socio-economic status, comorbid parent depression, obstetric complications) covariates?

2.3. Method

2.3.1. Search strategy

Our methods were registered in advance using the International Prospective Register of Systematic Reviews (PROSPERO; protocol number: CRD42019134977). Our search was conducted between July – September 2019, using Web of Science and Ovid (Embase, MEDLINE, Global Health, PsycINFO). The search was restricted to articles published in English. The following search terms were used to identify papers examining parent anxiety (NB., parent terms and anxiety terms were combined to restrict the number of search results, see supplementary materials in Appendix A for full search strategy):

- mother* or matern* or father* or patern* or parent* or *natal
  AND
- anx* or phobi* or “social* anx*” or “general* anx*” or neurotic* or obsessive* or panic or agoraphobi*

The following terms were included to identify papers that examined offspring outcomes and those that used a quasi-experimental design to control for potential genetic confounding (NB., to ensure that we identified all possible internalising outcomes examined to date, we did not restrict the search to pre-defined internalising outcomes):

- child* or adolescen* or teen* or youth* or young or offspring or infan*
  AND
- twin or twins or sibling* or adoption or adopted or “in vitro fertilization” or “assisted conception” or “cross-fostering” or “instrumental variable” or “quasi-experiment*” or causa* or genes or genetic or geno* or heritab*

The abstracts of all returned papers were screened independently by YA and MH. Studies were excluded if there was clear evidence that criteria were not met, with agreement from both researchers. The reference lists of relevant review papers were screened to identify any articles that were missed from the search, and further searches were made to identify published manuscripts from the authors of relevant conference abstracts. Full text screening for all retained studies was conducted by YA and MH, independently, to confirm eligibility. Disagreement was resolved through discussion with the senior researcher, TM. Data extraction from studies to be included in the meta-analysis was conducted by YA, checked by TM and TS.

2.3.2. Study selection

Published studies presenting empirical research were included if they:

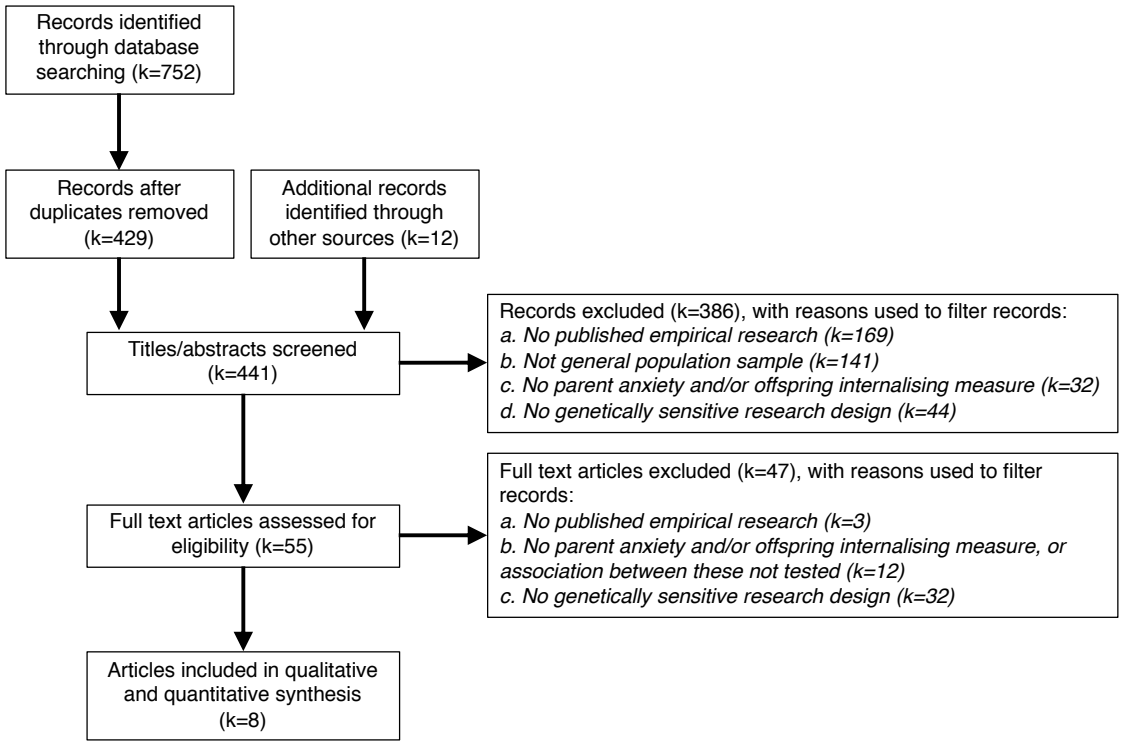
- involved a population of human parents and offspring (no sex or age restrictions)
- examined associations between parent anxiety (measured at trait, symptom or disorder level) and offspring internalising outcome/s (relating to one or more of: withdrawal, somatic complaints, anxiety, depression; Achenbach, Howell, Quay, & Conners, 1991)
- used a natural quasi-experimental research design to account for genetic relatedness in associations between parents and offspring (i.e., intergenerational genetically informed research designs, which enable researchers to control for participant relatedness; D'Onofrio et al., 2013)

Our search terms identified some studies of parental ‘stress’. We considered these to meet inclusion criteria if exclusively measuring *feelings* of stress (i.e., anxiety symptoms), not stressful life circumstances. Further, our search terms identified publications using ‘candidate gene’ approaches (using parent and child DNA) to control for the influence of specific shared genes in parent-offspring associations. Mental health phenotypes are complex traits; i.e., they are polygenic, influenced by hundreds of thousands of genetic variants across the genome, each exerting a very small effect (Chabris, Lee, Cesarini, Benjamin, & Laibson, 2015; Plomin, DeFries,

Knopik, & Neiderhiser, 2016). Therefore, studies accounting for the transmission of only a handful of genes (i.e., 'candidate genes') between generations are insufficient to control for genetic confounding in parent-child associations for mental health phenotypes (Duncan, Ostacher, & Ballon, 2019). The only genomic studies that thus met our inclusion criteria would be those taking a genome-wide, polygenic approach to quantifying intergenerational genetic relatedness. Furthermore, studies were excluded if they:

- focussed exclusively on populations with specific physical health problems (e.g., cancer, seizures, low gestational age) or a diagnosed developmental disorder (i.e., communication or learning disorders, motor disorders, attention-deficit/hyperactivity disorder, or autism spectrum disorders)
- involved an experimental exposure or intervention

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart



Of the 441 records screened, eight publications met our inclusion criteria (Figure 1). Of the excluded publications, seven included design features that accounted somewhat for bias by genetic confounding (Aktar, Majdandzic, de Vente, & Bogels, 2013; Capron et al., 2015; Henrichs et al., 2009; O'Connor, Heron, Golding, Beveridge, & Glover, 2002; O'Connor, Heron, Golding, & Glover, 2003; O'Donnell, Glover, Barker, & O'Connor, 2014; Van den Bergh & Marcoen, 2004).

These studies and our reasons for their exclusion are outlined in the supplementary materials (Appendix A). In brief, they were studies of prenatal anxiety exposure that used paternal anxiety symptoms as a 'negative control' for environmentally mediated prenatal transmission; and/or examined child exposure to parent state-level (i.e., current, transitory) anxiety symptoms, while controlling for parent trait-level (i.e., stable, longer-term) symptoms. We determined that they did not meet our criteria for a robust method to "account for genetic relatedness in associations between parents and offspring".

2.3.3. Data extraction

Data relating to sample characteristics, measurement protocol and statistical analyses were extracted from each publication that met our inclusion criteria. All genetically informed effect estimates were initially extracted. Where authors published multiple effect sizes for the same set of variables (e.g., where multiple analytic strategies were explored), we then had to decide which estimates to include in the meta-analysis to derive a meaningful pooled result. For the three publications examining prenatal anxiety exposure, one examined both continuous and binary coded data (Bekkhus et al., 2018). We selected results based on continuous scores, to be consistent with the other two publications (Gjerde et al., 2018; Rice et al., 2010). Two publications examining prenatal anxiety exposure reported separate effect estimates from analyses before and after adjusting for postnatal anxiety exposure (Bekkhus et al., 2018; Rice et al., 2010), while the third reported only adjusted results (Gjerde et al., 2018). These were all retained, to explore comparison of results that did versus did not attempt to isolate the effects of prenatal from postnatal exposure.

For the six publications of postnatal anxiety exposure, two reported both bivariate correlations and beta estimates from structural equation models (i.e., partial correlations) for the same set of variables, involving both cross-sectional and longitudinal datapoints (Ahmadzadeh et al., 2019; Brooker et al., 2015). It was not possible to extract data from the structural equation models in an informative way for inclusion in the meta-analysis, because saturated results were not presented in either publication (i.e., some paths had been trimmed from the models). Of the bivariate correlation analyses, longitudinal correlations (i.e., between parent anxiety exposure and future internalising outcomes in offspring) were not informative on their own as prospective associations, because they did not include correction for concurrent exposure to parental symptoms. As such, only the cross-sectional bivariate correlations were selected from these publications for inclusion in the meta-analysis. Cross-sectional effect estimates were available for inclusion in three of the four remaining publications examining postnatal anxiety exposure. For the one publication using only longitudinal data, the effect size with the shortest exposure-outcome time-lag was selected (9 months), to conserve consistency in the meta-analysis (Brooker et al., 2011). Two remaining longitudinal effect estimates (derived from two publications; Brooker et al., 2011; Gjerde et al.,

2018) were subsequently excluded, given that so few longitudinal estimates would be uninformative in the meta-analysis.

2.3.4. Effect size calculations

Pearson's correlation coefficient, *r*, was used as the uniform effect size across all studies, with confidence intervals computed for each estimate using the R package *compute.es* (Del Re, 2013). Pearson's *r* is an appropriate effect size to use for associations between continuous variables and results are easily interpretable (Rosenthal & DiMatteo, 2001). Non-independent effect sizes derived from the same or overlapping samples in a single publication (e.g., effect sizes at different child ages; see Figure S1 in Appendix A for an example) were aggregated using the R package *Mad* (for meta-analysis with mean differences; Del Re & Hoyt, 2014), to account for their correlation. Aggregation of correlated (i.e., non-independent) effect sizes within a single publication is required to prevent over-estimation of the precision of the pooled effect size in meta-analysis, which occurs when findings based on the same data are incorrectly treated as unique (Borenstein, Hedges, & Higgins, 2009; Gleser & Olkin, 2009). Aggregation of effect sizes within publications also prevents studies with more effect estimates from being given more weight in meta-analysis. Multilevel models are not appropriate to account for non-independence of effect size estimates within a single publication.

Non-independent effect sizes within each publication were aggregated first to create pooled effect sizes per publication ($r_{publication}$). In sensitivity analyses we aggregated non-independent effect sizes within each cohort, to create pooled effect sizes per cohort (r_{cohort}; Figure S1, Appendix A). Aggregation of non-independent effect sizes requires specification of their correlation. The magnitude of their correlation depends on the degree of overlap in the population sample, measures and timepoints used for each estimate. As is typically the case in a meta-analysis, the correlations between dependent effect sizes within each publication, and between publications, were unknown, meaning that we had to specify a likely value. Given the potential for this specified correlation to impact results, we conducted three sensitivity analyses for each aggregation, testing results using a full range of possible correlations for the association between dependent effect sizes: r=.10, .50 and .90.

2.3.5. Random Effects Models (REMs)

Meta-analytical models were conducted as multilevel random effects models (MREMs) using the R package *metaphor* (Viechtbauer, 2010). MREMs allow for between-study heterogeneity and can be used to test for moderating effects when data permits (i.e., methodological and observed covariates). First, MREMs were used to pool Pearson's *r* effect sizes from each publication ($r_{publication}$) examining prenatal, then postnatal, anxiety exposure. In this model, a source of variation was introduced for each cohort, to account for random variance (i.e., higher order

clustering) between cohorts, and for each publication within each cohort. Next, in a sensitivity analysis, we conducted standard REMs to pool aggregated, independent Pearson's *r* effect sizes from each cohort (r_{cohort}), separately for studies of prenatal and postnatal anxiety exposure. REM results were not biased by non-independent effect sizes, although they eliminated any information on the effects of moderating terms on the magnitude of associations within cohorts, relating to study design and sample characteristics in each publication.

Heterogeneity between effect sizes was assessed using the I^2 statistic, to examine whether study characteristics moderated the pooled effect size (Higgins, Thompson, Deeks, & Altman, 2003). The I^2 statistic is the percentage of total variation in study estimates that is due to heterogeneity, or between-study variability (values <25% indicate low; 25%-75% moderate; and >75% considerable heterogeneity). Publication bias was evaluated visually using funnel plots, plotting effect sizes against their standard errors. Symmetrically distributed data points indicate absence of publication bias. The low number of included studies yielded insufficient statistical power to test for asymmetry using Egger's linear regression (Egger, Davey Smith, Schneider, & Minder, 1997).

2.4. Results

2.4.1. Study descriptions

The eight retrieved papers were published between 2010 – 2019 (Ahmadzadeh et al., 2019; Bekkhus et al., 2018; Brooker et al., 2014; Brooker et al., 2011; Brooker et al., 2015; Eley et al., 2015; Gjerde et al., 2018; Rice et al., 2010), derived from four independent cohorts (N_{total}=12,990). Each cohort had one quasi-experimental research design applied (adoption, IVF, children-of-twins, sibling-comparison) and was mostly restricted to the study of one developmental period (infancy, middle childhood or adolescence; Tables 1–2). The sibling-comparison sample (derived from the Norwegian Mother, Father and Child Birth Cohort Study; MoBa) was far larger than all other samples combined.

Parent anxiety and offspring internalising symptoms were measured along continuous scales in all analyses extracted for the meta-analyses. All publications used correlation coefficients and/or standardised beta estimates to evaluate intergenerational covariance (see summary of the included analyses in Tables 1–2). Parent anxiety was measured by self-report, using five different measures of adult anxiety across publications. Seven child internalising constructs were assessed across the publications (e.g., combined internalising, negative affect, anxiety, social inhibition). Parents contributed at least partially to child symptom scores in all publications except one (where child social inhibition was measured solely by researcher observations; Brooker et al., 2011). Results derived from the sibling-comparison or IVF datasets were subject to the greatest risk of shared method variance, because *only* mothers' reports were used to construct variables in these cohorts. Two publications (each using the same adoption sample at different developmental stages) examined the directionality of effects between generations and analysed

mother-child and father-child associations separately (Ahmadzadeh et al., 2019; Brooker et al., 2015). A range of different measured covariates were accounted for in analyses, each attenuating the crude parent-offspring correlation to varying degrees.

Table 1. Studies of prenatal anxiety exposure: extraction of quasi-experimental data

Cohort	**Cardiff IVF study**	**Norwegian Mother, Father and Child Birth Cohort Study (MoBa)**	
Location	**United Kingdom**	**Norway**	
Design	**IVF "cross-fostering"**	**Sibling-comparison**	
N individuals per family unit	**2 (1 parent, 1 child)**	**3 (1 parent, 2 children)**	
Reference	**Rice, 2010**	**Bekkhus, 2018**	**Gjerde, 2018**
N family units	205	5935	11553
Exposure period (gestational weeks)	Prenatal (31-40)	Prenatal (17-30)	Prenatal (30)
Exposure measure (reporter)	Anxiety/stress: 1 item completed retrospectively, 11-point response scale (self)	Anxiety: 5 and 8 item Hopkins Symptom Checklist, 4-point scale (self)	Anxiety: 8 item Hopkins Symptom Checklist, 4-point scale (self)
Parent relationship to child	Mothers	Mothers	Mothers
Outcome period (child age years)	Middle childhood (4-10)	Infancy (0.5, 3)	Infancy (1.5, 3, 5)
Outcome measure (reporter)	Anxiety: 6 items based on DSM-IV, 3-point response scale (mother)	Infant difficulties: 9 item Infant Characteristic Questionnaire, 7-point scale (mother) Emotional difficulties: 10 item Child Behaviour Checklist, 3-point scale (mother)	Internalising: 13 item Child Behaviour Checklist, 3-point scale (mother)
Genetically informative analyses (estimates included in the meta-analysis) [a]	(1) Multiple regression (standardised β=.21, longitudinal) (2) Multiple regression (standardised β=.11, longitudinal)	(1) Multiple regression (standardised β=.07, .02, longitudinal) (2) Multiple regression (standardised β=-.03, -.00, longitudinal)	Multilevel regression (standardised β=.01; longitudinal) [b]
Measured covariates considered in the estimate extracted for meta-analyses [a]	(1) Child age, child sex, family social occupational class, antenatal complications (vaginal bleeding, admission to hospital for high blood pressure/oedema, maternal cigarette smoking, maternal alcohol use, infant plurality) (2) Child age, child sex, family social occupational class, antenatal complications (vaginal bleeding, admission to hospital for high blood pressure/oedema, maternal cigarette smoking, maternal alcohol use, infant plurality), maternal postnatal anxiety/depression	(1) None (2) Child sex, partner (dis)harmony, marital status, maternal education, antenatal complications (maternal prenatal cigarette smoking, maternal prenatal alcohol use, gestational age, birth complications, birthweight), somatic disease, maternal age, parity, maternal postnatal anxiety	Child age, child sex, parity, maternal postnatal anxiety/depression

[a] Numbering indicates separate, genetically informative analyses, where authors did versus did not adjust for postnatal anxiety exposure

[b] Regression coefficient standardised using the reported standard deviations (s) for the independent (x) and dependent (y) variables [$z\beta = \beta(sx/sy)$]

Table 2. Studies of postnatal anxiety exposure: extraction of quasi-experimental data

Cohort	**Early Growth and Development Study (EGDS)**				**Twin Offspring Study in Sweden (TOSS)**	**Norwegian Mother, Father and Child Birth Cohort Study (MoBa)**
Location	**United States of America**				**Sweden**	**Norway**
Design	**Adoption**				**Children-of-twins**	**Sibling-comparison**
N individuals per family unit	**2 (1 parent, 1 child)**				**4 (2 parents, 2 children)**	**3 (1 parent, 2 children)**
Reference	**Brooker, 2011**	**Brooker, 2014**	**Brooker, 2015**	**Ahmadzadeh, 2019**	**Eley, 2015**	**Gjerde, 2018**
N family units	361	361	349	305	871	11553
Exposure period (child age years)	Infancy (0.75)	Infancy (0.75)	Infancy (0.75, 1.5, .2.25)	Middle childhood (6, 7, 8)	Adolescence (11-22)	Infancy (0.5, 1.5, 3, 5)
Exposure measure (reporter)	Anxiety: 21 item Beck Anxiety Inventory, 4-point scale (self)	Anxiety: 21 item Beck Anxiety Inventory, 4-point scale (self)	Anxiety: 21 item Beck Anxiety Inventory, 4-point scale (self)	Anxiety: 20 item State-Trait Anxiety Inventory for Adults, 4-point scale (self)	Anxiety: 20 item Karolinska Scales of Personality, 4-point scale (self)	Anxiety: 8 item Hopkins Symptom Checklist, 4-point scale (self)
Parent relationship to child	Unspecified	Unspecified	Mothers, Fathers	Mothers, Fathers	Unspecified	Mothers
Outcome period (child age years)	Infancy (0.75)	Infancy (1.5, 2.25)	Infancy (0.75, 1.5, .2.25)	Middle childhood (6, 7, 8)	Adolescence (11-22)	Infancy (1.5, 3, 5)
Outcome measure (reporter)	Social inhibition: Observational tasks (researcher)	Internalising: 36 item Child Behaviour Checklist, 3-point scale (mother, father)	Negative affect composite: 11 item Infant Characteristics Questionnaire, 7-point scale; 36 item Infant Behaviour Questionnaire, 7-point scale; 19 item Toddler Behaviour Assessment Questionnaire, 7-point scale (mother, father), Observational tasks (researcher)	Anxiety: 13 item Child Behaviour Checklist, 3-point scale (mother, father)	Anxiety: 7 items from Child Behaviour Checklist, 3-point scale (mother, father); 7 items from Child Behaviour Checklist, 3-point scale (self)	Internalising: 13 item Child Behaviour Checklist, 3-point scale (mother)
Genetically informative analyses (estimates included in the meta-analysis)	Bivariate correlation (r=.00, cross-sectional)	Bivariate correlation (r=.23, longitudinal)	Bivariate correlation (r=.03, .02, .00, .19, .07, .08; cross-sectional)	Bivariate correlation (r=.16, .15, .20, .24, .11, 10; cross-sectional)	Children-of-twins structural equation model (standardised β=.25; cross-sectional)	Multilevel regression (standardised β=.05; cross-sectional) [a]

(continued)

Measured covariates considered in the estimate extracted for meta-analyses	None	None	None	None	Parent age, parent sex	Child age, child sex, parity, maternal depressive symptoms at each assessment (including prenatal), exposure and outcome at each assessment (including prenatal)
[a] Regression coefficient standardised using the reported standard deviations (s) for the independent (x) and dependent (y) variables [$z\beta = \beta(sx/sy)$]						

2.4.2. Meta-analysis

2.4.2.1. Prenatal anxiety exposure

MREM results showed a negligible and nonsignificant pooled effect size between prenatal anxiety exposure and infant internalising outcomes, using data from three publications that were corrected for genetic confounding and exposure to postnatal anxiety (*r*=.04, 95% CI -.07,.14; Figure 2A). Pooled estimates were equivalent in REM analyses using aggregated cohort data (Figure 2B). Two publications provided results that were unadjusted for postnatal anxiety exposure. REM analyses of these estimates revealed the pooled effect size to be larger than those using adjusted estimates, but still non-significant (*r*=.11, 95% CI -.05,.28). Because there were only three publications examining prenatal anxiety exposure, statistical power was insufficient to test for heterogeneity of effect sizes.

2.4.2.2. Postnatal anxiety exposure

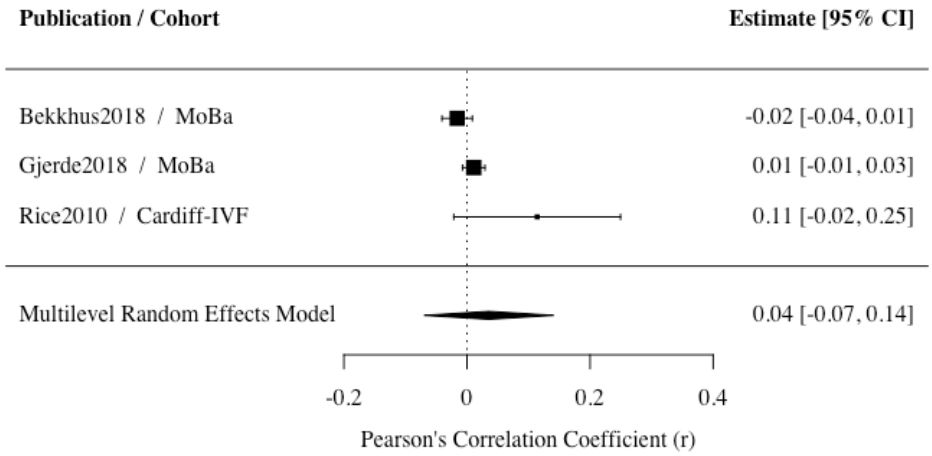
MREM results revealed a significant pooled effect size between concurrent anxiety exposure and offspring internalising outcomes after controlling for genetic confounding (*r*=.13, 95% CI .04, .21; Figure 3A). Results were comparable in analyses using effect sizes aggregated by publication and by cohort (Figure 3B). Results showed substantial levels of heterogeneity between publications (I^2=90, suggesting that 90% of the x^2 statistic was explained by variation between studies of postnatal anxiety exposure). Assessment of relevant moderators to identify sources of heterogeneity was not feasible, because the cohorts used were largely dissimilar in their sample and design characteristics. They could not be grouped and compared in meaningful ways and statistical power would have been insufficient to explore variance explained by higher-order clustering (a three-level REM to examine moderation by covariates requires meaningful variance between covariates; Konstantopoulos, 2011). Of note, most publications were conducted using an adoption design, meaning that authors could not report estimates that were free from

adjustment by genetic confounds (i.e., all adoption results are 'adjusted by design' for genetic relatedness, because parents and offspring are not genetically related). Therefore, we were unable to compare effect sizes across levels of adjustment (i.e., adjusted versus unadjusted for genetic confounds).

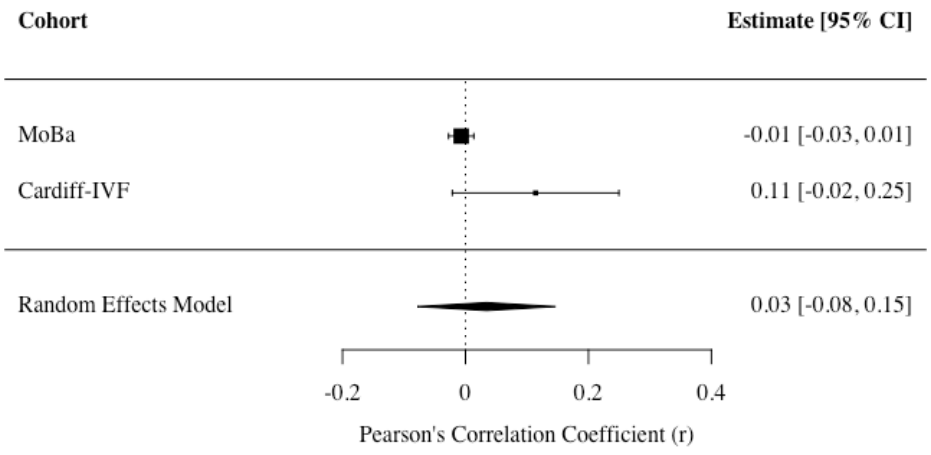
All presented models used aggregate effects sizes within publications/cohorts assuming a median correlation of *r*=.50, as suggested elsewhere (Borenstein et al., 2009; Del Re & Hoyt, 2014; Gleser & Olkin, 2009). Results were consistent across the three sensitivity analyses run for each effect size aggregation (*r*=.10/.50./90, by publication and by cohort; see Figure S2 in Appendix A).

Figure 2. The association between prenatal anxiety exposure and offspring internalising outcomes

A. Estimates pooled by publication, with multilevel clustering by cohort



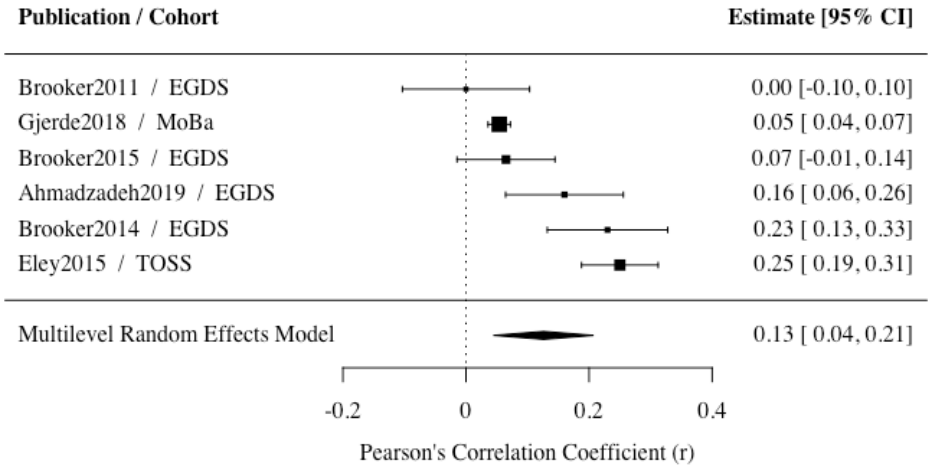
B. Estimates pooled by cohort



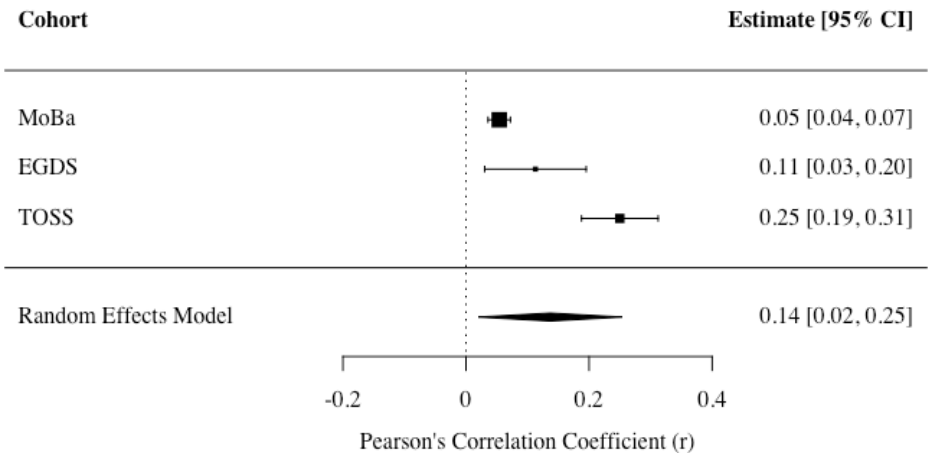
CI = Confidence Intervals; Cardiff-IVF = Cardiff In Vitro Fertilisation study; MoBa = Norwegian Mother, Father and Child Cohort Study.

Figure 3. The association between postnatal anxiety exposure and offspring internalising outcomes

A. Estimates pooled by publication, with multilevel clustering by cohort



B. Estimates pooled by cohort



CI = Confidence Intervals; EGDS = Early Growth and Development Study; MoBa = Norwegian Mother, Father and Child Cohort Study; TOSS = Twin Offspring Study in Sweden.

2.4.3. Additional observations

Within the publications examining prenatal anxiety exposure, only the IVF design yielded a significant, non-genetic association, for offspring anxiety in middle childhood (standardised β=.21; Rice et al., 2010). However, this effect was attenuated and no longer significant after postnatal anxiety exposure was controlled for (standardised β=.11). In the two publications using sibling-comparison designs, researchers found no significant associations in any of their reported

analyses with offspring during early childhood (standardised β range -.03–.07; Bekkhus et al., 2018; Gjerde et al., 2018).

As shown in Table 2, all effect sizes involving postnatal anxiety exposure were weak (standardised β and *r* values ranged .00–.25). However, structural equation models in two publications using adoption designs showed that parent and child symptoms could prospectively predict one-another across time, highlighting intergenerational, non-genetic, transactional effects during early and middle childhood (Ahmadzadeh et al., 2019; Brooker et al., 2015). Results from these publications showed differences for mother-child versus father-child effects. For example, stronger evidence for an effect of child symptoms on fathers' compared to mothers' anxiety was observed during infancy (Brooker et al., 2015); while an effect of child symptoms during middle childhood was only observed for mothers', not fathers' anxiety (Ahmadzadeh et al., 2019). The only publication using a sibling-comparison design for postnatal analyses showed that mothers' symptoms did not prospectively predict offspring internalising symptoms, after controlling for genetic relatedness.

2.4.4. Publication Bias

Studies with significant findings are more likely to be published in scientific journals, which increases risk of incorrect conclusions from the systematic reviews of published literature and risk of false positive or negative findings in meta-analytic results (Kicinski, Springate, & Kontopantelis, 2015). For example, non-significant intergenerational associations are unlikely to be published, meaning that parents may appear more similar to their offspring when judging by the published literature alone. Funnel plots for our data are shown in the supplementary materials (Figure S3, Appendix A), providing preliminary, albeit non-significant, evidence for publication bias. Only one publication reported null findings for any association between parent anxiety and offspring internalising, however the main focus of that study was on other phenotypes not relevant to this review, for which they had significant findings (Brooker et al., 2011).

2.5. Discussion

Following a systematic literature search we found only eight publications where authors used a quasi-experimental research design to control for genetic confounding in associations between parent anxiety exposure and offspring internalising outcomes. These used data from four independent cohort studies, where each cohort had a different quasi-experimental research design applied. Low homogeneity between publications from different cohorts yielded low statistical power to test for moderation by methodological (e.g., study design) or observed (e.g., child age) covariates. Results highlight a striking need for new research, without which we remain ill-equipped to understand why parent anxiety symptoms are associated with the development of offspring internalising problems.

2.5.1. Mother's prenatal anxiety symptoms were not associated with offspring internalising symptoms after controlling for genetic relatedness

Results from three publications, using data from two cohorts, indicated that prenatal exposure to maternal anxiety is not associated with offspring internalising symptoms via non-genetic mechanisms. Quasi-experimental research examining prenatal depression symptoms shows similar findings (also derived from the MoBa cohort evaluated in the present study; Hannigan et al., 2018). As such, quasi-experimental findings to date contradict existing literature on foetal programming in the context of family risk for internalising problems, which has been derived mostly from observational and/or animal studies (e.g., Aktar, Qu, et al., 2019; Glover, 2014; Lautarescu et al., 2020; O'Connor et al., 2014). We emphasise the need for new genetically informed investigations to produce a robust evidence base, looking across child development and into adulthood. Until new research is available, we encourage researchers and clinicians to consider the importance of genetic transmission and postnatal exposure in their work on maternal anxiety during pregnancy.

2.5.2. Concurrent associations between parent anxiety and offspring internalising symptoms remained significant after controlling for genetic relatedness

A small but significant association was found for concurrent anxiety exposure and child internalising symptoms, in quasi-experimental studies that accounted for parent-child genetic relatedness. This finding is consistent with a causal interpretation, potentially reflecting at least some direct, environmentally mediated influence between parents and offspring. However, this result is limited to cross-sectional data. It cannot inform on the direction of effects between parents and offspring, nor on the stability of associations across time. Meta-analyses of concurrent versus longitudinal associations were not feasible given the scarcity of available data.

Mixed findings were reported in the few publications that did include longitudinal analyses within their quasi-experimental design. Adoption data showed evidence consistent with parent anxiety predicting child internalising symptoms, within two year periods during early and middle childhood (Ahmadzadeh et al., 2019; Brooker et al., 2015). The same data also showed evidence for child-to-parent effects, mirroring results from longitudinal studies that do not control for genetic relatedness between parent and child (Elgar et al., 2003; Fanti et al., 2013; Villarreal & Nelson, 2018). However, researchers using a sibling-comparison design found that mothers' postnatal anxiety symptoms did not prospectively predict offspring internalising symptoms within a five-year-period (Gjerde et al., 2018). It is clear that further research is needed. Although we did not restrict our search by offspring age, we only found publications conducted during childhood. Genetically informed research on familial depression suggests maintenance of parent-offspring associations into adulthood (Kendler, Ohlsson, Sundquist, & Sundquist, 2018). It is unknown whether the same pattern holds for anxiety.

In sum, the data retrieved in our systematic search provide some evidence for non-genetic pathways between parent anxiety and concurrent offspring internalising symptoms during childhood, however longitudinal research is lacking and so the direction of effects between generations remains unclear. This is an important message for clinicians working with parents experiencing anxiety symptoms: we currently cannot tell with confidence whether parents' symptoms exert palpable, lasting influence on offspring internalising.

2.5.3. Considering the role of methodological confounding

2.5.3.1. Bias by quasi-experimental design

More research is required before we can test the extent to which effect estimates were biased by each quasi-experimental design used. The largest parent-offspring association that we found was derived from the only publication to examine adolescent offspring – also the only publication to use a children-of-twins design (Eley et al., 2015). We cannot tell whether this reflects influence of the developmental period, research design, and/or other factors. In children-of-twins research, the influence of genetic relatedness on a parent-offspring correlation will be underestimated if statistical power is low, thereby inflating the unconfounded residual estimate (Ahmadzadeh et al., in revision; McAdams et al., 2018). As such, statistical power issues could explain the relatively large effect size derived from the only children-of-twins publication (Eley et al., 2015). Conversely, the role of genetic relatedness in families can be overestimated in sibling-comparison research, thereby deflating the adjusted estimate. This is because confounding by genetic *and* environmental family factors are simultaneously corrected for, while assuming that symptoms in the exposed sibling do not influence symptoms in the non-exposed sibling (Lahey & D'Onofrio, 2010; Petersen & Lange, 2020). This could explain the relatively small effect sizes reported in the two sibling-comparison publications included in our meta-analyses (Bekkhus et al., 2018; Gjerde et al., 2018). It is also possible for both children-of-twins and sibling-comparison designs to overcorrect for genetic relatedness if genetic factors comprise an integral part of the causal pathway in parent-to-child environmental transmission, rather than acting as confounders across generations (McAdams, Rijsdijk, Zavos, & Pingault, 2020). Statistical limitations such as these are bypassed in adoption and IVF designs, where parents and offspring are not genetically related. However, these designs come at the cost of smaller (due to highly specific recruitment criteria) and potentially less-representative (only those who have experienced adoption or IVF) samples. Conducting new research using a range of quasi-experimental designs should help to balance the strengths and limitations of each, yielding more reliable and robust conclusions (Rutter & Quinton, 1984).

2.5.3.2. Measurement bias

It is likely that measurement bias accounts at least partially for the heterogeneity observed across our reported effect estimates. When working with the large samples required for genetically informative quasi-experiments, it can be methodologically and/or logistically impractical to include

lengthy assessments and more than one reporter per family. For example, prenatal symptoms in the IVF study were reported by mothers using a single item, several years after pregnancy, alongside mothers' reports of offspring internalising (Rice et al., 2010). Recall bias and shared method variance may have inflated the parent-offspring correlation in this sample. In the only publication to eliminate risk of shared method variance, parents' self-reports of anxiety were not associated with child symptoms (measured by researcher observations; Brooker et al., 2011) However, researcher observations of young offspring in artificial situations may not have been as reliable as parents' reports. Indeed, data from multiple reporters do not always converge. For example, in the adoption cohort we see low agreement between parent reports of offspring anxiety, with father-child anxiety associations only observed when using fathers' reports for both child and self (Ahmadzadeh et al., 2019). When new research becomes available, it will be informative to test for moderation by aspects of publication measurement protocol, to investigate influence on pooled results in MREM analyses. In the meantime, it will be important for researchers to consider the perspectives of multiple reporters where possible and maintain clarity as to the potential impact of measurement bias on results.

2.5.3.3. Use of observed covariates

In each publication, the nature, number and combination of observed covariates will have influenced the strength and meaning of the results. Authors attempted to correct their analyses in a range of ways across publications (e.g., regressing out the effects of age, sex and socio-economic-status, see Tables 1 and 2). Some effect estimates included in our meta-analyses included no correction for measured covariates and were arguably 'under-corrected' (e.g., adoption results that did not include correction for perinatal complications). In contrast, analyses in one publication using a sibling-comparison design involved use of several covariates (Gjerde et al., 2018). When our meta-analysis of concurrent anxiety exposure was computed without results from the sibling-comparison analyses (which comprised by far the biggest sample), it was reassuring to find that the pooled effect estimate only increased by r=.03 (see supplementary materials, Appendix A). Further, controls for anxiety exposure at different developmental stages requires consideration. In the case of chronic parental anxiety, collinearity becomes an issue for statistically differentiating exposure effects at different periods (e.g., prenatal versus postnatal anxiety effects). That is, if anxiety symptoms before and after the child's birth are highly correlated, controlling for variance in one period will remove variance in the other. This could explain why the prenatal anxiety association in the IVF study became non-significant after controlling for postnatal anxiety exposure (although analyses of postnatal exposure that included correction for prenatal symptoms did not find the same phenomenon, as residual postnatal symptoms remained predictive of offspring internalising; Ahmadzadeh et al., 2019; Brooker et al., 2015; Gjerde et al., 2018; Rice et al., 2010). Going forwards, we encourage researchers to report both unadjusted and adjusted results, as Bekkhus et al. (2018) did, alongside information on the variance explained by each covariate, to help in future research efforts to combine results.

2.5.4. Further avenues for research

2.5.4.1. Expanding analyses beyond parent-offspring dyads

The majority of research used in this review is focussed on mother-child dyads. Where possible, it will be informative to take a more holistic approach to genetically informed intergenerational research, considering fathers, siblings, extended family members and the myriad of social, economic and societal factors that can influence participants' mental health. For example, modelling both mother-child and father-child associations concurrently across time shows transactional influences between all individuals (Ahmadzadeh et al., 2019). Going forward, researchers could also include sibling effects in research and avoid randomly selecting only one child per family for analyses (or two differentially exposed siblings; Oliver & Pike, 2018). This could be possible in the Early Growth and Development Study (EGDS), where data are now collected on both birth and adoptive siblings (Leve et al., 2019). Information on multiple children per parent is also available in the Norwegian Mother, Father and Child Birth Cohort Study (MoBa), where siblings can be included in multiple-children-of-twins models (McAdams et al., 2018). These can be used to examine moderation by environments shared within families (e.g., family composition and social support) and between families (e.g., cultural and societal factors; McAdams et al., 2018), while also including data on two parents, to address issues surrounding assortative mating (Torvik et al., 2020). The consequences of parents' resemblance in anxiety has not yet been considered in genetically informed, intergenerational research. In sum, researchers should strive to move beyond analyses of only mother-child dyads, to ensure validity and generalisability of results across families.

2.5.4.2. Cohorts that were not designed for quantitative genetic research

The quasi-experimental designs used in this review require highly specific, large-scale family-samples. That we only identified eight publications, using data from only four cohorts, is telling of the challenges associated with collecting these data. Several publications that we excluded in our systematic search used data from large-scale population studies (e.g., Generation R and the Avon Longitudinal Study of Parents and Offspring) that are rich in phenotypic information but lacking the targeted recruitment required for traditional, pedigree-based genetic research (e.g., adoptive parents or twins with children; Capron et al., 2015; Henrichs et al., 2009; O'Connor et al., 2002; O'Connor et al., 2003; O'Donnell et al., 2014). Rapidly evolving methods in genomic research may soon provide novel opportunities for these cohorts, using participant DNA to examine intergenerational genetic transmission.

At present, genomic research for complex traits remains limited by a 'ceiling effect', whereby results reflect only the additive effects of genetic variants tagged on DNA arrays, excluding non-additive effects or rare variants (Cheesman et al., 2017). Until this is addressed, genomic methods cannot adequately control for genetic relatedness when examining associations between parent and child traits in a way that is comparable with the control achieved in adoption, sibling-

comparison or children-of-twins research. Future advances may include use of polygenic scores in parents and offspring, to examine the role of transmitted versus non-transmitted genetic variants in phenotypic associations across generations (Bates et al., 2018; Domingue, Belsky, Conley, Harris, & Boardman, 2015; Kong et al., 2018; Wertz et al., 2019). The principals of Mendelian randomisation may also be used to examine environmentally-mediated, parent-to-child causal pathways, using parent genes as instrumental variables (Lawlor et al., 2017). Further, genomic variance decomposition methods can be used to partition the influence of parent and offspring genetic influence on traits when genome-wide single nucleotide polymorphism (SNP) data have been collected from family members (Cheesman et al., 2020; Eaves, Pourcain, Smith, York, & Evans, 2014; Eilertsen et al., 2020). We may soon be able to decompose covariance in traits across generations using estimates of SNP-based heritability. With rapid advances in genomic research, we may be on the brink of a new era for advancing our understanding of familial risk for anxiety and internalising.

2.5.5. Limitations

Some limitations of our methodology require emphasis. To pool together all available data, we combined a mix of bivariate and partial correlations. This limited our ability to directly compare estimates between publications, where different adjustments were made for observed covariates. Further, we did not distinguish different types of internalising problems among offspring, but instead pooled data relating to child anxiety, negative affect, social inhibition and other emotional difficulties. We cannot tell whether findings would differ by child disorder subtype. This results from lack of available data, meaning we could not test for moderating terms in MREM models. Finally, all four cohorts included in the present meta-analysis were derived from populations in Northern Europe or North America, highlighting need for additional research to determine whether our findings are generalisable to other populations.

2.5.6. Summary

Quasi-experimental designs can help to control for the effect of genetic relatedness in similarities between parents and offspring. We sought to investigate whether associations between parent anxiety symptoms and offspring internalising symptoms can be explained via non-genetic mechanisms. We found the existing literature to be limited, with only eight genetically informed studies published, using data from only four cohorts. In a meta-analysis of the available data, we found no evidence to suggest that maternal prenatal anxiety symptoms exert influence on the development of offspring internalising symptoms via non-genetic mechanisms. However, we show that during childhood parent anxiety symptoms are associated with concurrent internalising symptoms in offspring via non-genetic mechanisms.

2.6. References

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3. Anxiety in the family: a genetically informed analysis of transactional associations between mother, father and child anxiety symptoms

This chapter is presented as a published paper. It is an exact copy of the open access, peer-reviewed publication. Supplementary materials for this chapter, as detailed in the text, are included in Appendix B (page 176).

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Anxiety in the family: a genetically informed analysis of transactional associations between mother, father and child anxiety symptoms

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Background: Anxiety in parents is associated with anxiety in offspring, although little is known about the mechanisms underpinning these intergenerational associations. We conducted the first genetically sensitive study to simultaneously examine the effects of mother, father and child anxiety symptoms on each other over time. **Method:** Adoptive parent and child symptoms were measured at child ages 6, 7 and 8 years from 305 families involved in the Early Growth and Development Study, using a prospective adoption design. Children were adopted at birth to nonrelatives, and composite data on internalising problems within birth families were used as a proxy measure of offspring inherited risk for anxiety. Structural equation models were fitted to the data to examine prospective associations between adoptive mother, father and child symptoms, whilst accounting for individuals' symptom stability over time. **Results:** Child anxiety symptoms at age 7 predicted adoptive mothers' anxiety symptoms at age 8. No mother-to-child or child-to-father effects were observed. These results were consistent in sensitivity analyses using only paternal offspring reports and using a second measure of child anxiety symptoms. Fathers' anxiety symptoms at child age 6 prospectively predicted child symptoms, but only when paternal offspring reports were included in the model. Composite data on birth family internalising problems were not associated with child anxiety symptoms. **Conclusions:** Results show environmentally mediated associations between parent and child anxiety symptoms. Results support developmental theories suggesting that child anxiety symptoms can exert influence on caregivers, and mothers and fathers may play unique roles during the development of child symptoms. Further research is needed on the role of genetic transmission associated with anxiety symptoms in biologically related families. In the meantime, researchers and clinicians should strive to include fathers in assessments and consider the effects of child symptoms on caregivers. **Keywords:** Anxiety; parent–child relationships; genetics; longitudinal; structural equation modelling.

Introduction

It is well established that anxiety disorders run in families, with strong evidence for associations between parent and child anxiety (Lawrence, Murayama, & Creswell, 2018; Micco et al., 2009; Sydsjo, Agnafors, Bladh, & Josefsson, 2018). However, the mechanisms underlying these associations remain unclear. Children of anxious parents can inherit genes associated with the development of anxiety from their parents (a genetic mechanism); anxious parents and children can behave in ways that promote anxiety in the other (environmental mechanisms); and negative environments shared by both generations can simultaneously influence anxiety in both. These mechanisms are not mutually exclusive. To better understand intergenerational anxiety associations in families, researchers should explore multiple mechanisms concurrently, requiring the use of genetically informed, longitudinal research.

Traditional twin studies suggest that childhood anxiety symptoms are moderately heritable (Boomsma, Van Beijsterveldt, & Hudziak, 2005; Trzaskowski, Zavos, Haworth, Plomin, & Eley, 2012). This infers that around half of the individual differences in vulnerability to anxiety can be explained by environmental influences, and half by genetics. When parents and children are genetically related, it follows that any parent–child anxiety correlation might be influenced by shared genes. Researchers have used a cross-sectional children-of-twins design to directly examine genetic mechanisms influencing intergenerational anxiety associations (Eley et al., 2015). Here, the correlation between parent and adolescent anxiety was not significantly confounded by genetic relatedness, indicating that the familial association could be attributable to environmental exposure to an anxious relative. However, it was not possible to identify the direction of effects between generations. Environmental parent-to-child anxiety transmission may occur as a result of maladaptive parenting and/or child observational and instruction-based learning (Aktar,

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Nikolić, & Bögels, 2017; Ginsburg & Schlossberg, 2002). Researchers have focussed particularly on the role of parent over-involvement (Aktar et al., 2017; Eley, Napolitano, Lau, & Gregory, 2010; Ginsburg & Schlossberg, 2002; Hudson, Comer, & Kendall, 2008; Murray, Creswell, & Cooper, 2009). Less attention has been paid to theoretical models of development which posit that intergenerational associations may be transactional (Bell, 1968). Child-to-parent anxiety effects have seldom been assessed. Therefore, whilst research indicates that the environment plays a significant part in the familial transmission of anxiety, our understanding of the underlying mechanisms remains limited.

To examine transactional associations between parents and children, we require longitudinal studies that enable parent-to-child and child-to-parent effects to be assessed simultaneously. The first genetically informed research on transactional effects between parent anxiety and child outcomes was conducted using the same prospective adoption sample as in the present manuscript; the Early Growth and Development Study (EGDS; Brooker et al., 2015). In the adoption design, *adoptive* parent and child associations are free from confounding by genetic relatedness. When children are adopted at birth to nonrelatives, as in the EGDS, *birth* parent and child associations act as a proxy measure of inherited genetic effects. Focussing on infant offspring in the EGDS sample, results demonstrated both parent-to-child *and* child-to-parent effects between adoptive parent anxiety symptoms and infant negative affect (Brooker et al., 2015). Like Eley et al. (2015), no evidence was found for genetic parent–child associations, using birth parent negative affect to model genetic transmission. In other samples, it has been suggested that child anxiety elicits 'extreme control' in mothers, with both phenotypes influenced by the *child's* genetic makeup (Eley et al., 2010); and mothers of clinically anxious children respond to child negative affect with greater intrusive involvement than mothers of nonanxious children (Hudson et al., 2008).

Given the focus on mother–child dyads in the existing literature, there are now growing efforts to investigate the role of fathers as well. A direct influence of paternal depression on offspring mental health has been reported in several (Class et al., 2012; Lewis, Neary, Polek, Flouri, & Lewis, 2017; Pemberton et al., 2010; Ramchandani et al., 2008) but not all (Tully, Iacono, & McGue, 2008) studies including fathers, which were not all genetically informed. Father–child anxiety associations have been seldom studied. Researchers suggest that mothers' and fathers' anxiety and behaviour may be differentially associated with offspring anxiety across development, with the father's role increasing over time (Connell & Goodman, 2002; Hudson et al., 2008; Moller, Majdandzic, & Bogels, 2015; Weijers, van Steensel, & Bögels, 2018). Evolutionary theory suggests that fathers encourage offspring to confront the external world, and children look more to fathers in threatening situations for clues on how to respond. Anxious fathers may not fulfil these roles, thereby influencing the development of child anxiety (Bögels & Perotti, 2011; Bögels & Phares, 2008; Paquette, 2004). Furthermore, as fathers typically adopt fewer care-giving responsibilities than mothers, they may be less susceptible to the emotional impact of offspring psychopathology (Bögels & Perotti, 2011; Weijers et al., 2018). Ideally, researchers should examine the role of both parents together, considering how all three individuals influence one another's mental health (Davies & Cicchetti, 2004). Such work should assess whether previously reported dyadic parent–child anxiety associations remain significant in mother–father–child analyses, which better reflect the social and genetic nature of most families.

We used the EGDS adoption sample to conduct the first study of transactional associations between parent and child anxiety symptoms during middle childhood. We follow-up on previous research showing that intergenerational anxiety associations between adolescent offspring and parents are under environmental influence (Eley et al., 2015). We expected to find similar results during middle childhood when anxiety disorders first begin to develop, whilst expanding on this to explore transactional intergenerational effects. We used age-appropriate anxiety measures in each generation, with two parents reporting on child anxiety. We controlled for passive genetic effects by examining children who were adopted at birth, and we explored the role of inherited effects using a composite measure of lifetime internalising problems among birth parents and their first-degree relatives. This composite was designed to reflect a single internalising liability factor, capturing multiple internalising symptoms and diagnoses across time, based on evidence for their strong genetic overlap and that persistent problems are under greater genetic influence (Caspi et al., 2014; Kendler et al., 2011; Krueger & Markon, 2006; Waszczuk, Zavos, Gregory, & Eley, 2014). We sought to understand whether lifetime risk reported in adulthood was associated with genetically influenced symptoms in biological offspring (Boomsma et al., 2005). We included birth parent, adoptive mother, father and child symptoms together in longitudinal models. We expected that results would differ by parent gender, but no further expectations were made as this is the first genetically informed, longitudinal study of transactional intergenerational anxiety associations.

Method

Participants

Participants were drawn from Cohort I of the EGDS, comprising 361 linked triads of adopted children, adoptive parents and birth parents (Leve et al., 2013). Cohort I recruitment ran from

2003 to 2006 with the help of 33 US adoption agencies across 10 states. All children were adopted domestically and placed with their adoptive families within 90 days of birth (mean age 3 days, *SD* 5 days). This study used data collected from adoptive parents when children were aged 6, 7 and 8 years, and from adult birth parents 18 and 54 months postpartum. All triads with same-sex adoptive parents were removed, to enable comparison of mother–child and father–child dyads, leaving a final sample of 305 families (43% female offspring) who were not missing on all data.

Ethical considerations

After receiving a complete description of their participation, all parents provided written informed consent for themselves, and adoptive parents consented for their child. Ethical approval was obtained from the three institutional review boards for the universities involved in data collection.

Offspring anxiety symptoms

Offspring anxiety symptoms were measured via adoptive mother and father report using the Anxious/Depressed subscale of the Child Behavior Checklist (CBCL); one of the most established measures of maladaptive behaviours during childhood, demonstrating strong psychometric features among children aged 1.5–18 years (Achenbach & Rescorla, 2004). Items focus on trait-level descriptions of anxiety, with 8 age-appropriate items in the preschool version (used in this study at child age 6) and 13 age-appropriate items in the school-age version (used at child ages 7, 8). All items were assessed via a Likert scale where 1 = 'not true' and 3 = 'very true'. Mean item scores were calculated for each reporter at each wave (mother α = .68–.78, father α = .65–.79), and average parent scores were used to reduce shared method variance. Parent reports correlated strongly on the preschool version and moderately on the school-age version (age 6/7/8 r = .86/.40/.39). Where results were missing from one adoptive parent, scores from the nonmissing parent were used alone (age 6/7/8 n = 40/42/65). In sensitivity analyses, offspring anxiety symptoms were assessed using adoptive mother and father reports separately, and with average mother–father scores on the Eley Anxiety Measure (described in Figure S1, Eley et al., 2003). Items in the Eley Anxiety Measure focus on clinical symptoms of anxiety disorders, in contrast to the trait-level descriptions included in the CBCL. Average scores were moderately correlated between the two measures (age 6/7/8, r = .54/.43/.65).

Adoptive parent anxiety symptoms

Adoptive parent anxiety symptoms were measured by self-report when children were aged 6, 7 and 8 years using the 20-item Trait Anxiety scale from the State-Trait Anxiety Inventory for Adults (STAI). The STAI is among the most widely used measures of general trait-level anxiety, demonstrating strong psychometric properties in adults (Spielberger, 1989). It is assessed against a four-point scale where 1 = 'almost never' and 4 = 'almost always' (mother α = .91–.92, father α = .91–.92). Items corresponded with the child CBCL items assessing trait-level anxiety, with both scales measuring self-confidence, feelings of inadequacy, nervousness and worries.

Offspring inherited risk

Offspring inherited risk was measured using a composite score previously designed for use in the EGDS (Marceau et al., 2015). Four indicators relating to internalising problems in the birth family were used to compute the score – derived from birth mother and father self-reported data 18 and 54 months postpartum. For the first three indicators, the Composite International Diagnostic Instrument (Kessler & Ustun, 2004) was used to create birth parent counts for lifetime symptoms and diagnoses, and age of onset, for 11 internalising disorders (major depression, recurrent brief depression, dysthymia, separation anxiety, adult separation anxiety, social phobia, agoraphobia with and without panic, panic disorder, specific phobia and generalised anxiety). Episodes of antenatal birth mother internalising were excluded and instead used in the calculation of obstetric complications. The fourth indicator comprised the number of first-degree relatives who had ever been diagnosed with an internalising disorder, derived from birth parent reports for each relative using the Family History-Research Diagnostic Criteria (Endicott, Andreasen, & Spitzer, 1977). The composite score was intended to be a more robust measure of inherited anxiety risk than any single assessment, given that internalising disorders load highly onto a single liability factor and show strong genetic overlap in adulthood (Caspi et al., 2014; Kendler et al., 2011; Krueger & Markon, 2006; Waszczuk et al., 2014). Indicators were entered to a principal component analysis (PCA) separately for each disorder, and extracted factor scores were aggregated to create the total. Missing data for variables in each PCA were imputed in R (using package missMDA) for up to 22% of birth mothers and 64%–70% of birth fathers, depending on the indicator. The score explained 34% of the variance for internalising in the full EGDS sample (N = 551, Eigenvalue = 2.69). For the present study: n = 268, M = −0.20, SD = 1.39, min = −3.81, max = 5.44, skew = 0.68, kurtosis = 3.83.

Covariates

Data on obstetric complications, adoption openness and child sex (male = 1, female = 2) were included in analyses as possible confounding variables. Birth mother reports and medical records relating to obstetric complications were collected 5 months postpartum. These data were used to calculate five indices of risk that were combined to create a weighted risk total score (Marceau et al., 2016). Adoption openness was characterised as the degree of contact, disclosure and frequency of communication between birth parents and adoptive families. Openness was measured six times from child age 5 months–6 years by birth mothers and adoptive parents using a seven-point scale, where 1 = 'very closed' and 7 = 'very open'. A mean standardised score was created at each time using data from each available parent's score (e.g. Ge et al., 2008).

Analyses

All anxiety variables were log transformed to correct for skew. Outliers were reduced to a maximum value of three standard deviations above or below the mean. Robust maximum likelihood estimation (MLR) in Mplus 7.4 was used to fit triadic auto-regressive cross-lagged structural equation models to the adoptive family data, computing maximum likelihood estimates for missing data. In these models, the auto-regressive paths account for stability over time. The cross-lagged paths account for prospective effects from one individual to another. Birth parent data were included as a proxy measure of offspring inherited risk for anxiety. Covariates were included in all associations involving birth parent, adoptive parent and offspring data at 6 years (the earliest measurement point).

Full unconstrained models were examined and nonsignificant cross-lag paths with the smallest standardised effect sizes were removed one-by-one, ensuring that model fit was not lost. Changes in model fit were assessed using chi-square difference tests, adjusting chi-square by the Satorra–Bentler scaling correction (SCR; as is required when using the MLR estimator in Mplus). Model fit was considered adequate if the root-mean

square error of approximation (RMSEA), comparative fit index (CFI) and Tucker–Lewis index (TLI) fell within recommended ranges (Hu & Bentler, 1999). In sensitivity analyses, models were rerun using the Eley Anxiety Measure for child symptoms, to investigate whether results were consistent across a second child construct. Next, models were rerun independently for each child informant to assess shared method variance. Results from the sensitivity analyses are included in Figures S1 and S2.

Results

Descriptive statistics are shown in Table 1 (birth parent data described in methods). Repeated-measures ANOVA suggested that adoptive mothers reported significantly higher levels of anxiety symptoms compared to adoptive fathers at ages 6 and 7 (6 years: $t(556) = 2.52$, $p = .01$; 7 years: $t(535) = 2.37$, $p = .02$; 8 years: $t(398) = 1.46$, $p = .14$). Fewer adoptive fathers participated compared to adoptive mothers and not all parents participated at every age, with attrition evident over time (see Table 1). By age 8, 7% of children scored within the borderline or clinical range for an anxiety disorder.

Cross-time within-measure pairwise correlations (Table 2, white boxes) showed moderate to strong continuity over time. Child anxiety symptoms were not associated with birth parent internalising (dark grey box). Child symptoms correlated significantly with current and future adoptive mother symptoms (light grey box, left), but adoptive mother symptoms did not correlate significantly with future child symptoms. Child anxiety symptoms correlated with adoptive father symptoms on fewer instances than for adoptive mothers (light grey box, right). Adoptive father symptoms correlated significantly with future child symptoms, but child symptoms did not correlate significantly with future father symptoms.

Table 1 Descriptive statistics for anxiety symptoms in adoptive families

Child age	*n*	Mean	*SD*	Min	Max
Adoptive Mother: (measure range 20–80)					
6 years	290	35.01	8.86	20.00	71.00
7 years	284	34.88	8.60	20.00	72.00
8 years	225	34.27	8.73	20.00	68.00
Adoptive Father: (measure range 20–80)					
6 years	268	33.14	8.63	20.00	59.00
7 years	253	33.13	8.44	20.00	57.00
8 years	175	32.95	9.34	20.00	62.00
Child: (measure range 0–16 at age 6; 0–26 at ages 7, 8)					
6 years	263	1.70	1.45	0.00	8.50
7 years	243	2.05	2.04	0.00	16.00
8 years	233	2.52	2.72	0.00	14.00

Child data represent average adoptive parent scores, using the preschool Child Behavior Checklist (CBCL) at age 6 and school-age CBCL at 7, 8. Scores were standardised to enable longitudinal comparisons. Adoptive parent symptoms did not change significantly (mothers: $F_{2,494} = 2.22$, $p = .11$; fathers: $F_{2,411} = 0.58$, $p = .56$) but child symptoms did ($F_{2,439} = 6.79$, $p < .001$). Child anxiety differed by sex only at age 6 ($t(261) = -3.04$, $p = .003$).

Figure 1 shows the final model in which all non-significant cross-lag paths were removed. Child anxiety symptoms at age 7 prospectively predicted adoptive mother anxiety symptoms at age 8 ($B = .16$). No significant mother-to-child effects were found. In contrast, adoptive fathers' anxiety symptoms at age 6 prospectively predicted child anxiety symptoms at age 8 ($B = .10$). No significant child-to-father effects were found. Results suggested that anxiety symptoms in adoptive mothers at the 7-year assessment prospectively predicted symptoms in adoptive fathers at 8 years ($B = .12$). Composite data on internalising problems among birth families were not associated with adopted child anxiety symptoms ($B = -.07$ to $.06$), and dropping this variable had no effect on model fit. Table S1 lists the fit indices for the constrained and unconstrained models.

Results were equivalent in bivariate models when mother–child and father–child dyads were analysed separately. Child sex was not significantly associated with adoptive parent anxiety symptoms but was significantly associated with child symptoms at age 6 ($B = .17$, 95% CI 0.08–0.27, $p = .003$). Obstetric complications and adoption openness were not significantly associated with the study variables, except for adoption openness at 5 months with birth parent composite data ($B = .22$, 95% CI 0.5–0.39, $p = .04$).

To evaluate the sensitivity of our results to alternative definitions of anxiety, we reran analyses using a different scale of mother- and father-reported child anxiety (the Eley Anxiety Measure, Table S2). Child-to-mother, father-to-child and mother-to-father effects were found again, although the father-to-child effect was identified at an earlier timepoint (Figure S1). We also reran analyses using father-only report of child anxiety, then mother-only report. The child-to-mother effect remained when child symptoms were reported by fathers, but the father-to-child effect was not found when child symptoms were reported by mothers (Figure S2).

Discussion

This is the first genetically informed study to assess transactional associations between parent and child anxiety symptoms during middle childhood. Using adoption data from the EGDS, we showed that child anxiety symptoms at age 7 prospectively predicted maternal, but not paternal, anxiety symptoms. This was significant in models where adoptive mother, father and child anxiety symptoms were all able to influence one another, whilst accounting for autoregressive effects. No mother-to-child effects were found. Results were consistent across two child anxiety constructs, using both maternal and paternal reports. When including paternal child reports, results suggested that paternal anxiety symptoms could prospectively predict child anxiety symptoms

Table 2 Pairwise correlations between adoptive mother, father and child anxiety symptoms and composite birth parent internalising data

		Birth Parents	Adoptive Mother			Adoptive Father			Adopted child		
		(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)
(2)	6 years	–.04									
(3)	7 years	–.06	**.81****								
(4)	8 years	.02	**.67****	**.68****							
(5)	6 years	–.09	**.13***	.12	**.17***						
(6)	7 years	**–.15***	.07	.10	.09	**.81****					
(7)	8 years	**–.18***	**.17***	**.23***	.14	**.72****	**.73****				
(8)	6 years	–.05	**.16***	**.17***	**.15***	.11	.11	.15			
(9)	7 years	.07	.07	**.15***	**.21***	.11	.10	.11	**.47****		
(10)	8 years	-.05	.13	.13	**.20***	**.17***	.13	**.24***	**.57****	**.67****	

Data transformed and standardised *$p < .05$, **$p < .001$.

from age 6. We did not find an association between offspring anxiety symptoms and our composite measure for birth parents' family history and lifetime symptoms, diagnoses and age of onset for 11 internalising disorders.

Whilst we know that intergenerational anxiety transmission is likely to be under environmental influence (Eley et al., 2015), this is the first study to show that such transmission can run from children to mothers during middle childhood. This adds to the growing body of evidence that children are active players within their environment, capable of exerting influence on their caregivers (Bell, 1968). It was reassuring to find that the child-to-mother effect remained consistent in sensitivity analyses: first using a separate child anxiety construct, and second when child symptoms were reported by adoptive fathers only. Previous analyses in this sample showed that infant fussing and crying predicted father anxiety (Brooker et al., 2015); however, we did not find the same for child internal symptoms during middle childhood. Our results suggest that mothers were at higher risk than fathers for being affected by offspring symptoms. Because mothers typically provide more day-to-day child care than fathers, they are perhaps more exposed and attuned to offspring anxiety, which can be worrying for parents (Bögels & Perotti, 2011; Hudson et al., 2008; Weijers et al., 2018). Therefore, having an anxious child may be more anxiety provoking for mothers compared to fathers. Given that mothers' over-involvement is associated with child anxiety (Aktar et al., 2017; Eley et al., 2010; Ginsburg & Schlossberg, 2002; Hudson et al., 2008; Murray et al., 2009), we could next explore whether these parenting behaviours develop *in response* to child anxiety and are associated with *subsequent* increases in maternal anxiety.

Like existing research on paternal depression (Class et al., 2012; Lewis et al., 2017; Pemberton et al., 2010; Ramchandani et al., 2008), we identified significant father-to-child anxiety effects, which were not also found for mothers. This is noteworthy given the wealth of previous research focussed on mother-to-child transmission, although our father-to-child effect was not replicated at the same ages using the Eley Anxiety Measure (Figure S1) nor when child symptoms were reported by adoptive mothers only (Figure S2). It is a strength in our research that we were able to compare perceptions of offspring anxiety across two parents, who may identify different aspects of the complex trait in their child (see Boomsma et al., 2005 for further discussion). Whilst we note that shared method variance appeared more pronounced for father compared to mother reports of self and child (Table S3), we believe that it would not provide a complete picture if fathers' perspectives were excluded. Results derived from paternal reports of child anxiety are in line with the evolutionary theory that fathers have a potentially important role to play in guiding their child's approach to exploring the world and responding to threat (Bögels & Perotti, 2011; Bögels & Phares, 2008; Paquette, 2004). Whilst researchers have previously examined differences in the *magnitude* of mother–child and

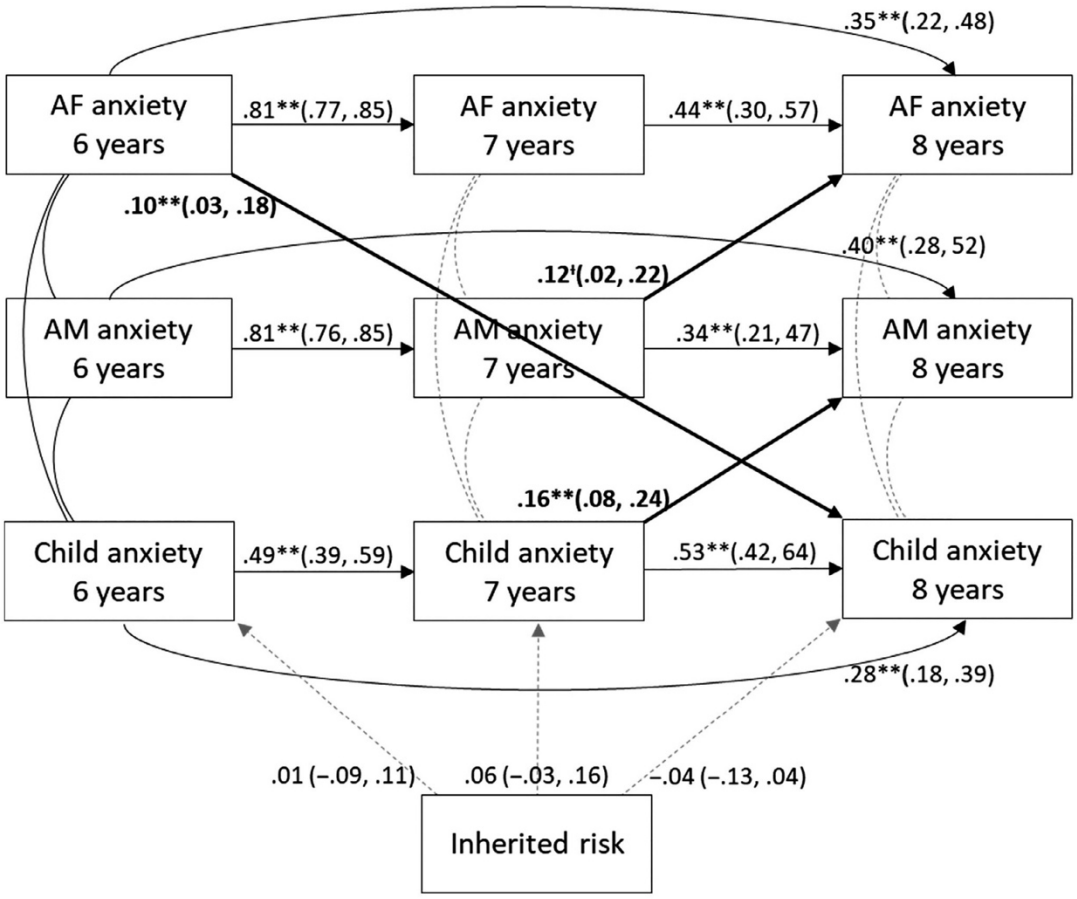

Figure 1 Results from the constrained structural equation model examining associations between adoptive father (AF), mother (AM) and child anxiety symptoms. Standardised parameter estimates ǂp = .05, **p < .001 (95% CI). Composite birth parent internalising data included as a proxy measure for child inherited anxiety risk. Nonsignificant cross-lag paths are dropped, remaining nonsignificant paths shown in dashed lines. Covariates are not displayed. Model fit statistics shown in Table S2

father–child psychopathology associations (Connell & Goodman, 2002; Weijers et al., 2018), we suggest that differences may lie in *directionality*. It will be of interest to explore these associations at later stages of development, considering whether results reflect diverging roles for primary and secondary caregivers (with parents able to swap between these) rather than parent gender differences. The marital relationship is also implicated in this family systems process (Bögels & Brechman-Toussaint, 2006; Davies & Cicchetti, 2004), supported by our reported mother-to-father effect. We could next examine whether a transactional cycle of environmental transmission exists longitudinally, where family members repeatedly influence one another, jointly contributing to the maintenance of familial anxiety symptoms.

Nonsignificant paths with negligible effect sizes were found between child anxiety symptoms and our composite measure for internalising problems within birth families, which acted as a proxy for inherited effects. This is consistent with the two relevant studies to date, where no evidence was found for a genetic effect on intergenerational associations involving parent anxiety (Brooker et al., 2015; Eley et al., 2015). However, it is possible that these studies, along with our own, were underpowered to detect genetic effects. Equally, measures of inherited effects in adoption studies could lack validity. Although moderate heritability estimates are reported for anxiety symptoms during middle childhood (using the same measures as in this manuscript; Boomsma et al., 2005; Trzaskowski et al., 2012), it could be that the same genes influencing anxiety symptoms in children are not the same as those acting in adult parents. In support of this, longitudinal research (again using the CBCL) shows genetic innovation and attenuation on anxiety from

child to adulthood (Kendler, Gardner, Annas, et al., 2008; Kendler, Gardner, & Lichtenstein, 2008; Waszczuk et al., 2014). In the present study, we aimed to maximise our chances of indexing a proxy measure of inherited risk that was related to offspring anxiety. We used a broad composite of birth parents' family history and lifetime symptoms, diagnoses and age of onset for 11 internalising disorders, which show strong genetic overlap at both the diagnosis and symptom level with one another (Kendler et al., 2011; Waszczuk et al., 2014). When no associations were found with offspring anxiety, we explored broadening our measure with additional information on birth parent substance use and externalising, to reflect genetic risk for a single psychopathology dimension (Caspi et al., 2014). Results remained unchanged, indicating that child anxiety symptoms could not be predicted by birth parent psychopathology (results available on request). Further research experimenting with different approaches to the measurement of inherited risk will be needed, whilst also examining the possibility of moderation by familial risk (i.e. gene–environment interaction).

Strengths of this study include the longitudinal and genetically informed design, and involvement of both mothers and fathers. As in all research, there are limitations to consider. We imputed over 64% of data for birth fathers, who provide half of offspring genes but who are difficult to recruit in adoption studies. Measurement error likely reduced the association between child anxiety symptoms and our composite birth parent internalising score, especially given that this scale for inherited risk is yet to be validated. New analyses show that birth father participation in the EGDS was related to adoption openness only, not other demographic variables, and total attrition at 8 years was not related to demographic variables (Marceau et al., in press). Risk of bias due to shared method variance was increased by the attrition of more adoptive fathers than mothers, but this did not undermine the child-to-mother effect that remained significant when using paternal reports of child symptoms in triadic models. Since child anxiety differed by sex at age 6, the slight weighting towards male offspring in our sample (43% female) should also be considered. We do not investigate the specific environmental mechanisms that underpin the reported intergenerational associations, and we did not account for factors outside of the parent–child relationship that may also be influential. Considering the generalisability of our sample, results may be biased towards American families with high socioeconomic status (Leve et al., 2013), and adopted children who are at higher risk of experiencing prenatal adversity and inheriting genes associated with psychopathology (Cadoret, 1990). We did not find evidence for an effect of obstetric or genetic factors, although our results cannot disprove their influence. The adoption design relies on the assumption that adoption openness (controlled for in our analyses) and selective placement will have minimal effect on results. Previous EGDS research found no significant correlations for personality, cognitive and economic characteristics between birth and adoptive parents, which are unlikely to be subject to evocative gene–environment effects (Leve, Neiderhiser, Scaramella, & Reiss, 2008). Results may differ within clinical samples where parents and children are at the extreme end of the anxiety symptom distribution. Nevertheless, we provide useful information about many parents and children who experience symptoms of anxiety but who are not yet included on clinical registers. Our results correspond with a clinical study where child anxiety influenced mothers but not fathers (Hudson et al., 2008).

To our knowledge, this is the first genetically informed study to test the theoretical hypothesis that both parents and children can be implicated in perpetuating intergenerational anxiety associations. We present novel evidence for an environmentally transmitted, prospective effect of child anxiety symptoms on mothers' symptoms during middle childhood. We suggest that parents and children may influence each other in different ways, with preliminary evidence that children are more susceptible to the effects of fathers' than mothers' symptoms. Further research aiming to replicate our findings across methodologies and populations will help to validate these results, whilst further investigating the role of genetic transmission between biologically related parents and children. In the meantime, researchers and clinicians should strive to include fathers in assessments and consider the effects of child symptoms on caregivers, to better understand the intergenerational transmission of anxiety symptoms.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Figure S1. Results from the first sensitivity analysis, with child anxiety measured using the Eley Anxiety Measure.
Figure S2. Results from the second sensitivity analysis, with child anxiety measured using (a) father and (b) mother reports separately on the CBCL anxious/depressed subscale.
Table S1. Model fit indices for the unconstrained and constrained structural equation models.
Table S2. Descriptive statistics for the Eley Anxiety Measure.
Table S3. Pairwise correlations between adoptive parent and adopted child anxiety symptoms, across four indices of child anxiety symptoms (by measure and parent reporter).

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Key points

- Anxiety disorders are known to run in families; however, little is known about how this happens.
- We compared children who were adopted at birth to both their biological and adoptive parents, to explore genetic and environmental anxiety transmission in families during middle childhood.
- Child anxiety symptoms at age 7 predicted adoptive mothers' symptoms at age 8 in all analyses. Adoptive fathers' symptoms predicted child symptoms if paternal offspring reports were included in the model.
- Child anxiety symptoms were not associated with the proxy measure for inherited risk – which indexed birth parents' family history and lifetime symptoms, diagnoses and age of onset for 11 internalising disorders.
- Clinicians should include fathers in assessments and consider the effects of child symptoms on caregivers, to better understand the environmental transmission of familial anxiety.

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4. Parental criticism and adolescent internalising symptoms: associations remain after accounting for shared genetic effects

This chapter is adapted from a manuscript that is currently undergoing the process of peer-review. Supplementary materials for this chapter, as detailed in the text, are included in Appendix C (page 180).

Ahmadzadeh, Y. I., Eley, T. C., Hannigan, L., Creswell, C., Lichtenstein, P., Spotts, E. L., Ganiban, J. M., Neiderhiser, J. M., Rijsdijk, F., McAdams, T. A. (in revision). Parental criticism and adolescent internalising symptoms: Associations remain after accounting for shared genetic effects. *Journal of Child Psychology and Psychiatry*.

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4.1. Abstract

Background: Parental criticism is correlated with internalising symptoms in adolescent offspring. This correlation could reflect confounding by genetic relatedness, if the same genes influence behaviours in both parents and offspring. We use a Children-of-Twins design to assess whether parent-reported criticism and offspring internalising symptoms remain associated after controlling for shared genes. To aid interpretation of our results and those of previous Children-of-Twins studies, we examine statistical power for the detection of genetic effects and explore the direction of possible causal effects between generations.

Methods: Data were drawn from two Swedish twin samples, comprising 876 adult twin pairs with adolescent offspring and 1030 adolescent twin pairs with parents. Parent reports of criticism towards their offspring were collected concurrently with parent and offspring reports of adolescent internalising symptoms. Children-of-Twins structural equation models were used to control for genetic confounding in the intergenerational association between parental criticism and adolescent internalising.

Results: Parental criticism was associated with adolescent internalising symptoms after controlling for genetic relatedness. No significant role was found for shared genes influencing phenotypes in both generations, although power analyses suggested that some genetic effects may have gone undetected. Models could not distinguish the causal direction of possible psychosocial effects between generations.

Conclusions: The association between parent-reported criticism and adolescent internalising symptoms could not be attributed to genetic confounding in this sample. Parental criticism may be involved in psychosocial family processes in the context of adolescent internalising. Future studies should seek to identify these processes and provide clarity on the direction of potential causal effects.

4.2. Introduction

Internalising symptoms are common during adolescence, encapsulating comorbid problems relating to anxiety and depression (Merikangas & Avenevoli, 2002). Subthreshold internalising disorders cause substantial impairment during adolescence, yielding a major public health burden (Roberts, Fisher, Turner, & Tang, 2015). If left untreated, problems can persist into adulthood, taking a chronic course and exerting significant impact on social, emotional and economic outcomes (Betts et al., 2016; Goodman, Joyce, & Smith, 2011). Research suggests that parent-child relationships are important for adolescent adjustment (Laursen & Collins, 2009), during formative years of increasing autonomy and parent-child separation (De Goede, Branje, & Meeus, 2009). Parental criticism of adolescents has received attention as a possible mechanism relevant to their development of internalising symptoms (Asarnow, Tompson, Woo, & Cantwell, 2001; Frye & Garber, 2005; Nelemans, Hale Iii, Branje, Hawk, & Meeus, 2014; Silk et al., 2009; Tompson et al., 2010).

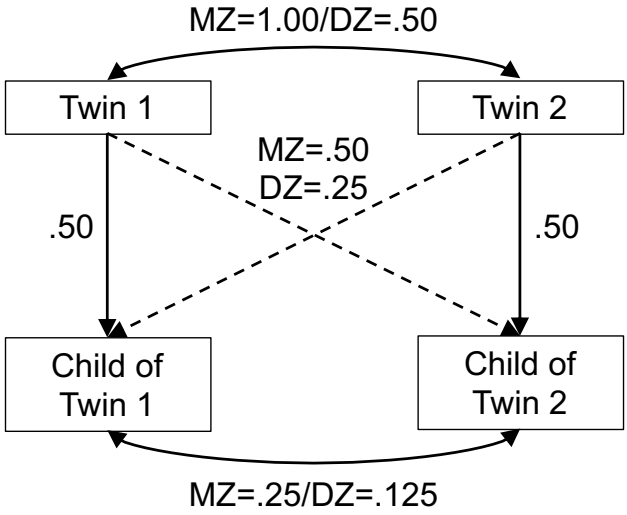
Parental criticism is characteristic of distressed or unsupportive interaction patterns within parent-child dyads (McCarty, Lau, Valeri, & Weisz, 2004). It is typically assessed using coded speech samples (e.g., Frye & Garber, 2005), or parent-report questionnaires (e.g., Nelemans et al., 2014). Associations between parental criticism and adolescent internalising problems may be driven by social interactions, such that parental criticism influences, or is influenced by, mental health difficulties in offspring (Hughes & Gullone, 2008). That is, parental criticism may contribute to the development of internalising symptoms in offspring and/or reflect the parent's reaction to distressing child behaviours. However, the relationship between parental criticism and adolescent internalising may be confounded by common causal variables, including genetics.

All human characteristics, including parenting behaviours and psychiatric symptoms, are influenced in part by genetics (Klahr & Burt, 2014; Plomin, DeFries, Knopik, & Neiderhiser, 2016; Polderman et al., 2015). Because offspring inherit genes from their parents, shared genetic factors may at least partially account for correlations in their behaviour. Genes linked to complex behaviours tend to have highly diffuse effects (Plomin et al., 2016), so the same genes could influence both internalising symptoms during adolescence and parenting behaviours in adulthood. If true, then it is important to control for the role of genetic relatedness in families, to better understand the extent to which parent and offspring behaviours may be *causing* one another.

The influence of genetic relatedness in families can be estimated and controlled for using causal inference designs. The Children-of-Twins design is one such example (McAdams et al., 2014). Here, adult identical (monozygotic, MZ) and fraternal (dizygotic, DZ) twin pairs and their offspring are compared for any given set of behaviours. In families of MZ twins, offspring are equally related to both their parent and their aunt/uncle (genetic correlation=.50 for both; Figure 1), although they share their immediate rearing environment only with their parent. In families of DZ twins, offspring are more genetically related to their parent (.50) than to their aunt/uncle (.25). So, if offspring

behaviours are more correlated with aunt/uncle behaviours in MZ versus DZ families, then genetic influence on the intergenerational correlation is inferred. If offspring behaviours are more correlated with parent versus aunt/uncle behaviours, then influence of the immediate rearing environment is inferred.

Figure 1. Genetic correlations between family members in the Children-of-Twins design for both monozygotic (MZ) and dizygotic (DZ) twin families



Existing Children-of-Twins research suggests that associations between adolescent internalising symptoms and parents' emotional overinvolvement (Narusyte et al., 2008), harsh punishment (Lynch et al., 2006) and parent-offspring relationship quality (Hannigan et al., 2018) are not confounded by genetic relatedness at all. One study exists on parental criticism specifically, in relation to offspring somatic symptoms, again showing that genetic relatedness does not explain any of the association (Horwitz et al., 2015). These results are somewhat surprising, given what we know of the highly diffuse effects of genes linked to complex traits. Indeed, power calculations to accompany Children-of-Twins research would be an advantage, to clarify our ability to adequately detect and control for genetic influence in each analysis. These have not been presented in the existing literature, so findings remain difficult to critically interpret. Further, only one of the aforementioned papers included analyses designed to explore the direction of possible causal effects (i.e., for associations not confounded by genetic relatedness) between generations (Narusyte et al., 2008). Results suggested a stronger influence of child internalising problems on parents' emotional overinvolvement, compared to the reverse, although again results are undermined by uncertainty regarding their statistical power to adequately detect genetic confounding.

Statistical power in Children-of-Twins designs depends on several factors, each of which can limit accuracy to detect the role of genetic transmission in parent-child associations. Factors include the magnitude of the phenotypic parent-child correlation; proportion of the correlation attributable to genetic overlap; magnitude of relatedness in avuncular pairs (Figure 1 dashed lines); sample size; ratio of identical and fraternal twins; heritability of the parent and offspring behaviours; and power to detect heritability within each generation (McAdams et al., 2018; Verhulst, 2017). These factors vary for different samples and variables. If power is not sufficient to detect genetic influence in Children-of-Twins analyses, then intergenerational covariance will appear unconfounded (McAdams et al., 2018). Previously published Children-of-Twins studies may have been underpowered, resulting in the overestimation of non-genetic effects. This has not been addressed in previous research.

We used a Children-of-Twins design to examine whether the association between parental criticism and adolescent offspring internalising symptoms remains after controlling for genetic mechanisms. We explore statistical power in our sample to detect an effect of genetic transmission between generations. Where evidence was found for non-genetic associations between parents and offspring, we investigated the direction of possible causal effects between generations.

4.3. Method

4.3.1. Participants

Data from two samples were combined for an Extended-Children-of-Twins (ECoT) design (as used in several previous Children-of-Twins studies, e.g., Hannigan et al., 2018; Narusyte et al., 2008): (1) a Children-of-Twins sample where the twins were adult parents with adolescent offspring, and (2) a sample of adolescent twin pairs with one parent per pair.

4.3.1.1. Children-of-Twins sample

Data were drawn from the Twin and Offspring Study in Sweden (TOSS; Neiderhiser & Lichtenstein, 2008), comprising 387 MZ and 489 DZ twin families. Families consisted of same-sex adult twin pairs (mother-mother or father-father), with one genetically related adolescent child per twin. Each twin had been cohabiting with a partner (usually spouse) for a minimum of five years. Cousins (the offspring) were the same sex and did not differ in age by more than four years. 37% of twins (parents) and 52% of offspring were male. Mean ages were 44.8 years for twins (SD=4.9; range 32-60) and 15.7 years for offspring (SD=2.4; range 11-22). We conducted sensitivity analyses excluding data from twin families where either offspring was >19 years (n=25), given that these offspring could be considered young adults and thus less likely to be directly exposed to parental criticism.

4.3.1.2. Adolescent twin sample

Data were drawn from Wave 3 of the Swedish Twin Study of Child and Adolescent Development (TCHAD; Lichtenstein, Tuvblad, Larsson, & Carlstrom, 2007). Wave 3 was chosen to match the adolescent ages and measures in the TOSS. The sample comprised 416 MZ adolescent twin pairs and 614 DZ pairs (299 same-sex DZ pairs). One parent was included per twin pair. 49% of twins and 13% of parents were male. Twins (adolescents) had a mean age of 16.7 years (SD=0.47; range 15-17).

4.3.2. Measures

4.3.2.1. Parental criticism

Parents reported on critical perceptions and behaviours towards their adolescent offspring, using the 10-item critical remarks subscale of a validated Expressed Emotion measure (Hansson & Jarbin, 1997). Self-reported questionnaires of parental criticism are useful in research to assess parents' own view of their feelings and experiences with the child. Data collection and coding costs less compared to interview assessments (Hale et al., 2011). Here, parents responded using a five-point Likert scale to indicate how often they agreed with each critical statement, e.g., "S/he makes me irritated", "It is hard for us to get along" and "I find faults with him/her".

4.3.2.2. Adolescent internalising symptoms

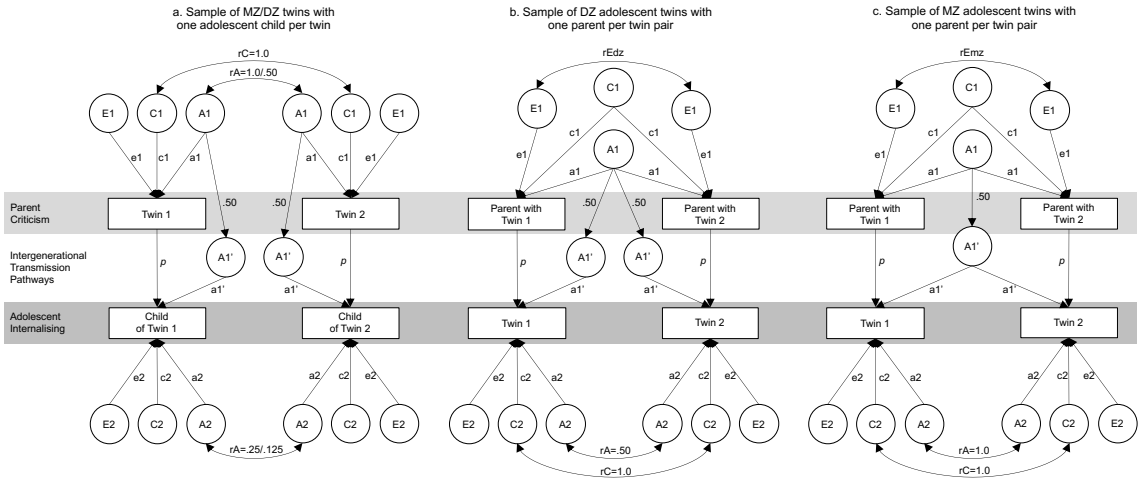
Adolescent internalising symptoms were reported by parents and adolescents using the 30-item Internalising scale of the Child Behaviour Checklist and Youth Self-Report, respectively (Achenbach, 1991a, 1991b). These corresponding parent and child assessments use the same three-point Likert scale and were moderately correlated in both samples (r=.36/.42 in TOSS/TCHAD). The broad internalising scale is the sum of the narrow syndrome scales for anxious/depressed, somatic and withdrawn behaviours, which share most of their genetic aetiology during adolescence (Waszczuk, Zavos, Gregory, & Eley, 2014). Parent and adolescent reports capture adolescent internalising phenotypes from different perspectives, with different biases associated with each method (De Los Reyes & Kazdin, 2005). We derived composite scores from a mean of parent and adolescent scale scores, to incorporate all available information. Including parent reports for all study variables could inflate the parent-offspring correlation via shared method variance. Therefore, we also conducted supplementary analyses using only self-reports for adolescent internalising.

4.3.3. Analysis

The effects of child age and sex were regressed out from all variables. Variables were then log transformed to correct for skew (see Table S1, Appendix C) and standardized. Structural equation models were fitted using maximum likelihood estimation in the R (version 3.6.1) programme OpenMx (version 2.15.5; Neale et al., 2016). Data from different family types (comprising MZ or

DZ, adult or adolescent twins) were specified separately in a single model (see Figure 2 for model specification). This model derived estimates for three sets of influences: (1) genetic and environmental influences on parental criticism, (2) covariance between the generations that is attributable to genetic versus non-genetic influences (which includes social effects), and (3) genetic and environmental influences on offspring internalising symptoms.

Figure 2. Model specification for decomposing the association between parental criticism and adolescent internalising symptoms



A1=additive genetic effects on parent criticism; C1=shared-environmental effects on parent criticism; E1=nonshared environmental effects on parent criticism; A2= additive genetic effects specific to adolescent internalising symptoms; C2=shared-environmental effects on adolescent internalising symptoms (cannot be estimated using cousin data); E2=nonshared environmental effects on adolescent internalising symptoms; A1′=genetic effects common to parent criticism and adolescent internalising symptoms; p=residual phenotypic association between parental criticism and adolescent internalising symptoms; rEmz/rEdz=freely estimated correlations to allow the parenting of adolescent Twin 1 and Twin 2 to differ from one another, while also ensuring that these within-person correlations can differ across adolescent zygosity (panels b and c) and can differ from adult MZ twin correlations (panel a). The pathway between A1 and A1′ is fixed to .50 because children inherit 50% of their parent's genes. Variance=1 for all latent factors.

Genetic and environmental influences on parental criticism were estimated using adult twin pairs. We quantified the influence of additive genetic (A1), common environmental (C1) and non-shared environmental (E1) effects on parental criticism, as in the regular twin design (Plomin, DeFries, & Knopik, 2012). Within-pair resemblance for parental criticism in adult MZ twin pairs can result from A1+C1 (Figure 2a). In DZ families, the parental twin correlation reflects their lower level of genetic resemblance (.50*A1+C1). This difference allows us to estimate all genetic and environmental parameters on parental criticism.

Intergenerational *covariance* was decomposed using comparisons of avuncular and parent-offspring correlations for MZ and DZ twins with children. Genetic sharing for avuncular pairs in MZ families is equal to parent-child genetic sharing. Genetic sharing is just .25 in the avuncular pairs in DZ families. This difference allows us to estimate the relative contribution of genetic influence on the intergenerational association. Genetic covariance between the parent and child behaviours was modelled via the a1' pathway (Figure 2a). Any residual intergenerational association was estimated via the *p* pathway, where influence of the immediate family environment is captured.

Comparing correlations between the offspring of MZ and DZ twins (i.e., cousins) allowed us to estimate genetic (A2) and non-shared environmental effects (E2) on offspring internalising symptoms. This is because cousins in MZ families have a higher genetic correlation (.25) than cousins in DZ families (.125). However, relatively low genetic sharing between cousins means that genetic influences on offspring traits can go undetected, due to low power. Because cousins do not share a home environment, they cannot inform on the influence of common environments on offspring traits (C2). Therefore, the adolescent twin dataset was used to additionally inform on the aetiology of offspring internalising symptoms. Twin pairs have higher genetic sharing compared to cousins, so yield greater power to detect A2, and can inform estimates of C2.

Parental criticism in the adolescent twin dataset contributed to estimates of the phenotypic parent-child correlation (Figure 2b-c). These data did not inform on the decomposition of parent trait aetiology, nor the decomposition of intergenerational covariance. The same parent reported on their criticism of each twin; therefore, A1 and C1 correlations were fixed to unity for parents of adolescent twins (Figure 2b-c, upper panel). The following paragraph describes two novel features that differentiate our model from those used in previous studies combining adult and child twin datasets.

We specified data from DZ and MZ adolescent twins separately, to reflect that MZ twins inherit the same genes from their parent (Figure2c), whereas DZ twins each inherit a random 50% (Figure 2b). This means that covariance between adolescent MZ twins includes A1', whereas covariance between DZ twins includes .25*A1'. This specification was not included in previously published studies (e.g., Narusyte et al., 2008). Further, we included parameters to distinguish within-parent correlations in the adolescent twin sample from MZ parent correlations in the adult twin sample (McAdams et al., 2018). These parameters (rEmz and rEdz) also allowed the within-parent correlations to differ between parents of MZ and DZ adolescent twins, to account for differences in evocative effects from MZ and DZ pairs (Avinun & Knafo, 2014). In previous research, correlations between the parenting of MZ twin pairs with children (Figure 2a, upper panel); within-person correlations for parenting of DZ twins (Figure2b, upper panel); and within-person correlations for parenting of MZ twins (Figure2c, upper panel) were all constrained to be the same (A1+C1). In our model specification, parameters rEmz and rEdz allow these to differ without biasing A1+C1 estimates, which derive from the Children-of-Twins sample.

The significance of model parameters in our complete model (i.e., combining specifications across Figure2) was tested by creating sub-models where paths were consecutively fixed to zero. χ^2 difference tests and Akaike's Information Criterion (AIC) were used to assess whether sub-models yielded significantly worse fits to the data. All models were re-run using adolescent self-reports alone for child internalising symptoms.

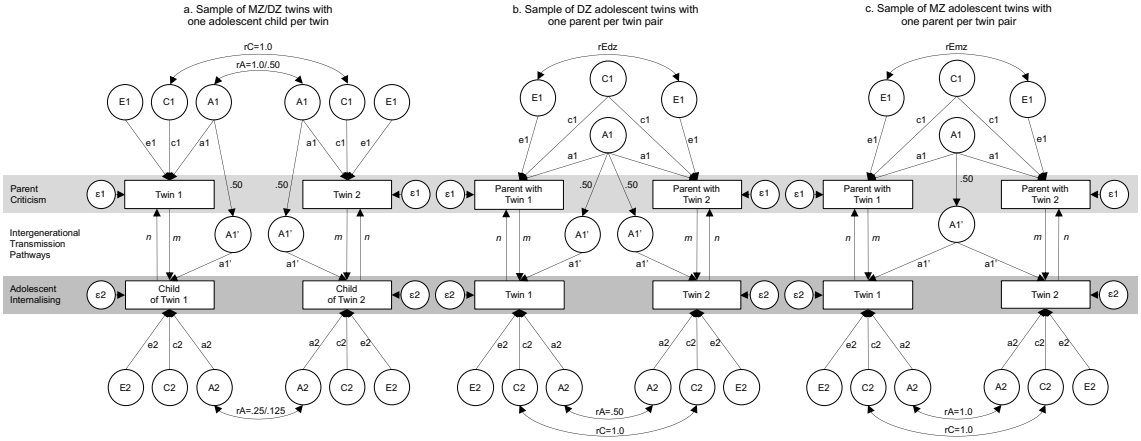
4.3.3.1. Power to detect genetic transmission effects (A1')

Accurate estimation of A1' (genetic contribution to the parent-child correlation) relies upon adequate statistical power. Estimation of *p* is inflated in models with inadequate power to detect A1', because *p* is the residual parent-offspring covariance after accounting for A1'. Therefore, we examined statistical power in our sample to detect an A1' of varied magnitudes. We simulated data to match our sample characteristics and systematically altered the strength of A1', noting the corresponding change in observed statistical power to detect it. We chose to conduct power analyses post-hoc rather than a priori. This is because it is difficult to estimate power to detect a single parameter a priori in large models when all parameters can affect one another (we estimate 8 paths concurrently), often in unpredictable, or at least non-intuitive, ways (Verhulst, 2017).

4.3.3.2. Direction of causation for phenotypic effects (*p*)

The *p* pathway is usually modelled as running from parent-to-child, although any child-to-parent effects are also captured. We tested a reciprocal causation version of the Children-of-Twins model, to examine the direction of causation for intergenerational effects indexed by the *p* pathway. Reciprocal causation can be modelled using cross-sectional family data for traits that differ in their aetiology (i.e., relative magnitudes of direct genetic and shared environmental influences; Duffy & Martin, 1994; Heath et al., 1993). When there is a causal relationship between two traits, and these traits differ in their aetiology, the covariance between the traits can be used to determine the direction of causation. For example, if X causes Y, and X is more heritable than Y, then the covariance between X and Y will be driven by genetic factors. As such, the covariance decomposition between X and Y can be used to trace the origins of their association. Put another way, the variance components of X can be thought of as instrumental variables in their prediction of Y, as they only become associated with Y via causal influence of X on Y (McAdams, Rijsdijk, Zavos, & Pingault, 2020). We used the model specification introduced by Narusyte et al. (2008) for Children-of-Twins data, where causal intergenerational paths run from parent-to-adolescent (m) *and* adolescent-to-parent (n) traits, alongside the A1' path for genetic transmission (see Figure 3). We made the same amendments to the model specification as discussed above for the unidirectional model (i.e., we include rEmz and rEdz parameters; and specify the model to ensure that MZ twin children share an identical A1' factor).

Figure 3. Model specification for a two-sample reciprocal causation Children-of-Twins model, used to decompose the association between parental criticism and adolescent internalising symptoms



A1=Additive genetic effects on parental phenotype; C1= shared-environmental effects on parental phenotype; E1=nonshared environmental effects on parental phenotype; A1'=genetic effects common to parental phenotype and offspring phenotype; A2=genetic effects specific to offspring phenotype; C2= shared-environmental effects on offspring phenotype (not estimable using cousin data); E2=nonshared environmental effects on offspring phenotype; m=phenotypic effect of parent on offspring; n=phenotypic effect of offspring on parent; rEmz/rEdz=freely estimated correlations to allow the parenting of adolescent Twin 1 and Twin 2 to differ from one another, while also ensuring that these within-person correlations can differ across adolescent zygosity (panels b and c) and can differ from adult MZ twin correlations (panel a). Measurement error (ε1 and ε2) contributes directly to the variance of both phenotypes.

4.4. Results

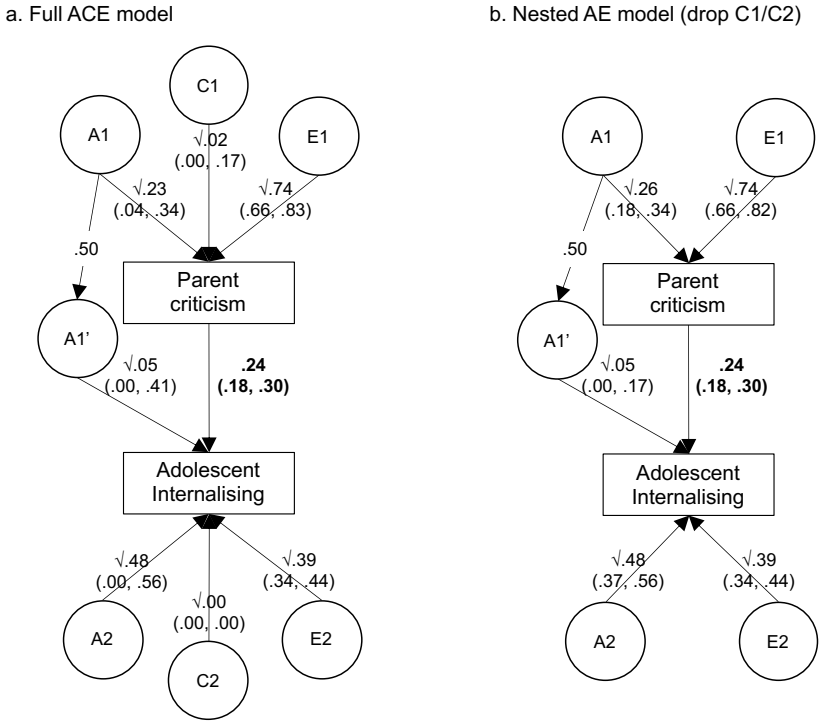
Table S1 (Appendix C) shows descriptive statistics for all measures. For adult twins, correlations in parental criticism were greater for MZ (.26) compared to DZ (.14) pairs, suggesting influence of parents' genes on parents' criticism (Table 1). Parent-child correlations (.29, set to be equal across family types) were over twice the magnitude of avuncular correlations in MZ (.12) and DZ (.06) families. This shows stronger correlations between individuals who lived together, indicating influence of their immediate family environment. Further, the stronger avuncular correlation in MZ versus DZ twin families could suggest a role for genetic transmission. For adolescent pairs, correlations in internalising symptoms were greater for MZ (.60) versus DZ (.31) twins; and cousins in MZ (.17) versus DZ (.09) families. This suggests influence of adolescents' genes on adolescents' internalising symptoms. Results were unaffected by the exclusion of data from the 25 families that included offspring aged 19–22 years. A similar pattern of results was found in models using only self-report data for adolescent internalising, although intergenerational correlations were smaller (Table S2, Appendix C).

Table 1. Correlations in monozygotic (MZ) and dizygotic (DZ) families

	MZ twin families	DZ twin families
Parental criticism		
Twin correlation [a]	.26	.14
Parental criticism and offspring internalising symptoms		
Parent-child correlation [b]	.29	.29
Avuncular correlation [a]	.12	.06
Offspring internalising symptoms		
Cousin correlation [a]	.17	.09
Twin correlation [c]	.60	.31

[a] From the Children-of-Twins sample, TOSS. [b] From the TOSS and the adolescent twin sample, TCHAD. [c] From the TCHAD.

Figure 4. Model results, showing the association between parental criticism and adolescent offspring internalising symptoms



A1=additive genetic effects on parent trait; A2=additive genetic effects specific to adolescent trait; A1′=additive genetic effects common to parent and adolescent traits (path from A1 to A1′ is fixed to .50 because offspring inherit 50% of their parent's genes); C1/C2=shared environment effects on parent/adolescent trait; E1/E2=nonshared environmental effects on parent/adolescent trait. Variance components are displayed, with the residual intergenerational association in bold (standardised path beta coefficient). The relative contribution of A1' in explaining the phenotypic parent-child correlation is calculated by multiplying the genetic paths connecting each trait, divided by the total phenotypic correlation (r=.29).

4.4.1. Model Fitting

Model results are depicted in Figure 4. C1 and C2 did not significantly account for measure variance, so were subsequently dropped. Their exclusion resulted in a more parsimonious model, without significant changes to model fit (Table S3, Appendix C). Heritability of parental criticism and adolescent internalising symptoms were estimated at 26% and 53% respectively. For the intergenerational association, the A1' variance component was not significantly different from zero (β=√.05, 95% CI .00-.41). The residual intergenerational pathway (*p*; presented as a standardised beta estimate for direct comparison with the phenotypic parent-offspring correlation) was positive and significant (β=.24, 95% CI .18-.30). Subsequent nested models reinforced this observation. Specifically, the intergenerational association could be adequately explained by a model excluding genetic transmission, but not by a model including only genetic transmission (Table S3, Appendix C). The conclusions drawn from the models remained consistent when using self-report data for adolescent internalising (Figure S1, Appendix C).

Table2. Exploring statistical power to detect genetic confounding between parental criticism and adolescent internalising symptoms (phenotypic correlation=.29)

	Specified/estimated parameters						%*r*Ph attributable	Power to detect A1'
	E1	A1	E2	A2	A1'	*p*	to A1'	(α=.05)
Study model	.74	.26	.39	.48	.05	.24	13	.26
Simulated models	.74/.75	.26/.26	.39/.41	.00/.01	.53/.53	.11/.11	62	1.0
	.74/.75	.26/.25	.39/.41	.10/.11	.43/.42	.13/.13	54	1.0
	.74/.75	.26/.25	.39/.41	.20/.22	.33/.31	.15/.15	48	1.0
	.74/.75	.26/.25	.39/.41	.30/.32	.23/.20	.17/.17	39	.98
	.74/.75	.26/.25	.39/.41	.35/.36	.18/.15	.19/.19	33	.93
	.74/.75	**.26/.25**	**.39/.41**	**.39/.40**	**.14/.11**	**.20/.21**	**29**	**.82**
	.74/.75	.26/.25	.39/.41	.40/.41	.13/.10	.20/.21	28	.78

We simulate data for 876 adult twin pairs with one child per twin and 1030 adolescent twin pairs with one parent per pair. Parameters are specified based on study results, where parental criticism heritability was .26 (A1) and adolescent internalising heritability was .53 (A1'+A2). Each row represents a new model. A1' specification is varied across models to manipulate the percentage of rPh (phenotypic correlation) attributable to genetic confounding. Corresponding changes are made to A2 and p specifications, to preserve heritability estimates and rPh in each model. Variance components are shown for latent factors (E1, A1, E2 etc.), whereas p is a standardised path coefficient (beta). Bolded text shows the model where 80% power to significantly detect A1' was reached.

4.4.2. Power to detect genetic transmission effects (A1')

To evaluate statistical power in our sample to detect genetic confounding we simulated a dataset to match the parameters in our final model. We examined how great the variance explained by A1' must be to harness ≥80% power to detect it, keeping total parent and child heritability estimates and parent-child covariance static (Table 2). There was ≥80% power to detect an A1' estimate of .11 or greater (Table 2, bold row). This would account for 29% of the phenotypic parent-child correlation. Therefore, results suggest that *at least* 71% of the association between parental criticism and offspring internalising symptoms was not attributable to genetic transmission in this sample. The small A1' estimate in Figure 4b *could* be a true finding for the role of genetic confounding (accounting for 13% of the phenotypic parent-child correlation), but statistical power was not sufficient to confirm it.

Statistical power was lower in models using only self-report data for adolescent symptoms, owing to the weaker phenotypic parent-child correlation. Here, there was 82% power to detect an A1' estimate of .12, accounting for 47% of the phenotypic parent-child correlation (Table S4, Appendix C). Therefore, results suggest that *at least* 53% of the association between parental criticism and adolescent-reported internalising symptoms was not attributable to genetic confounding.

4.4.3. Direction of causation for phenotypic effects (*p*)

Given that the association between parental criticism and adolescent internalising symptoms withstood correction for genetic relatedness, we applied a reciprocal causation version of our Children-of-Twins model (Narusyte et al., 2008), to explore whether the residual association was better explained by parent-to-adolescent or adolescent-to-parent effects. In this instance we were unable to distinguish a direction of causation. Whilst a genetic transmission only model (Table S5, Model 6; Appendix C) was a significantly worse fit to the data than the full model (in agreement with our unidirectional model), it was possible to drop either the parent-to-adolescent (m) pathway *or* the adolescent-to-parent (n) pathway without compromising model fit. This was true when comparing back to the full model (Table S5, Models 4 and 5 compared to Model 1; Appendix C), and when comparing back to the model with no genetic transmission (Models 7 and 8 compared to Model 3).

4.5. Discussion

Parent reported criticism towards adolescent offspring remained significantly correlated with adolescent internalising symptoms after controlling for confounding by genetic relatedness. Both parental criticism and offspring internalising symptoms were heritable, but no evidence for genetic covariance between them was found. Specifically, at least 71% of the parent-offspring association existed independently of shared genes, possibly arising from mechanisms in the immediate family environment. However, statistical power to detect genetic confounding was lower when examining a weaker parent-offspring correlation, derived when using only adolescent self-reports of

internalising symptoms. We did not examine the possibility of sex differences due to limited statistical power, and further work in other samples is needed to explore the directionality of intergenerational effects.

Previous Children-of-Twins studies examining offspring internalising outcomes suggest that genetic relatedness does not confound associations with parents' harsh punishment (Lynch et al., 2006), parent-offspring relationship quality (Hannigan et al., 2018), nor parental criticism (Horwitz et al., 2015). This is surprising, given that these behaviours are heritable and genes influencing complex traits show highly diffuse effects (Plomin et al., 2016). However, previous studies did not include power analyses for the detection of genetic transmission, so their findings remain ambiguous. Here we demonstrate that our primary finding (i.e., that the association between parental criticism and adolescent internalising symptoms remains significant after controlling for genetic relatedness) is not attributable to a lack of statistical power. Because previous studies used either the same sample as us (Hannigan et al., 2018; Horwitz et al., 2015), or samples of a similar size (Lynch et al., 2006), our power analyses indicate that their results are likely valid (though this is contingent on comparable phenotypic correlations and heritability estimates). We suggest that the presentation of power analyses in future Children-of-Twins research will aid interpretation of findings. It is also important to explore how decisions regarding methodology (e.g., measurement protocol) may impact on statistical power and interpretation of results.

We incorporated data from both parent and offspring reports of adolescent internalising symptoms, which were moderately correlated. Their partial agreement could reflect both shared perspectives and unique insights, alongside perceptual and reporting biases. For example, adolescents may report symptoms that are unknown to their parents, while parents may identify symptoms that adolescents have not yet recognised or do not wish to disclose (De Los Reyes & Kazdin, 2005). However, using parent reports for all study measures can inflate parent-child correlations via shared method variance. Supplementary analyses using only adolescents' self-reports of internalising symptoms showed consistent findings with our primary analyses, although the phenotypic parent-child correlation was attenuated (.29 to .18). Previously reported correlations are similar to ours, for example r=.22-.30 between coded speech samples for parental criticism and maternal reports for adolescent internalising (Frye & Garber, 2005), with lower correlations (r=.02-.24) reported when adolescents rate their own symptoms (Nelemans et al., 2014). We show that statistical power to identify genetic confounding is lower for smaller parent-child correlations. When r=.18, we had 80% power to detect a genetic effect accounting for ~50% of the parent-child correlation, rather than ~30%. Variation in research methodology can ultimately exert influence on the interpretation of results.

Overall, our findings support existing research that has not been genetically-informative, suggesting that parental criticism may be relevant to the environment in which adolescent internalising symptoms present (Asarnow et al., 2001; Frye & Garber, 2005; Nelemans et al., 2014; Silk et al., 2009; Tompson et al., 2010). However, we could not discern a direction of

causation between parent and offspring variables. This could be explained by a number of interrelated possibilities. The causal mechanism between phenotypes can be multifaceted (Duffy & Martin, 1994). As such, it could be that both parent-to-adolescent (m) *and* adolescent-to-parent (n) causal paths were operating in tandem. Further, the aetiological structure of our phenotypes may have been too similar to distinguish reciprocal causation (Duffy & Martin, 1994; Heath et al., 1993). Although adolescent internalising symptoms were more heritable than parental criticism in our data, it is possible that their aetiologies were not different enough to be distinguishable in our sample. This is supported the overlapping confidence intervals for parent and offspring trait heritability (A1 and A2) when A1' was dropped from the model (see Model 3 in Table S5, Appendix C). It may have been easier to distinguish the 'm' and 'n' paths if C2 were significant, because C2 would impact upon the parent-offspring covariance structure via the child-to-parent 'n' path. Causality between variables, in either direction, is a major assumption in direction of causation analyses (McAdams et al., 2020). Although we show that the association between parental criticism and adolescent internalising symptoms was not confounded by genetic factors in our sample, influence by common causes in the nuclear family environment (e.g., neighbourhood stressors, socio-economic factors, or other family members) remained possible. Influence by non-genetic confounders may have contributed to our inability to distinguish intergenerational causal paths.

Three complementary study designs could help to identify parent and/or offspring driven causal effects, if they are present. First, child twin studies inform on the extent to which *child* genes influence, or evoke, the parenting they receive (Klahr & Burt, 2014). We found some evidence for child-to-parent processes, as parents' reports of criticism were almost twice as correlated for MZ (.73) versus DZ (.43) adolescent twin pairs, suggesting that adolescents' genetically influenced behaviours evoked parental criticism. Further, adult twin data shows that parent-to-child effects are possible, as parents' genes also influence their parenting behaviours (Klahr & Burt, 2014). To date, the only Children-of-Twins study to directly test the direction of causation between parenting and adolescent internalising found evidence for child-based evocative effects (Narusyte et al., 2008), although we present corrections to their model specification. Overall, twin findings do support the possibility of transactional associations between adolescent internalising symptoms and parental criticism.

Second, longitudinal studies have generally identified transactional associations between parental criticism and adolescent internalising symptoms (Frye & Garber, 2005; Nelemans et al., 2014; Silk et al., 2009). One study with six time-frames showed that adolescent internalising was more predictive of parent-reported criticism (using similar questionnaire items as in this study), compared to the reverse (Nelemans et al., 2014). Whilst the association between aspects of the home environment and offspring depression remains relatively stable from childhood into adolescence, the role of offspring genetic influences increases in adolescence. As such,

adolescents may influence their environments, and thus the parenting they receive, to a greater degree than is seen in younger children (Hannigan, McAdams, & Eley, 2017).

Third, studies that take an experimental or intervention-based approach can help to delineate parent-to-child and child-to-parent effects. For example, parental displays of controlling behaviours in experimental settings leave children feeling less capable on a given task, with this effect moderated by child trait anxiety (Thirlwall & Creswell, 2010). Others show that parenting skills training can reduce internalising symptoms among young offspring (Cartwright-Hatton, McNally, White, & Verduyn, 2005), suggesting parent-to-child effects. Conversely, improvements in parenting are observed following treatment of adolescent anxiety (Silverman, Kurtines, Jaccard, & Pina, 2009), suggesting child-to-parent effects. As such, it is important to recognise that the direction of causation in associations between parenting and adolescent outcomes is unlikely to run solely from parents to offspring.

Some limitations of this study require consideration. Despite our sophisticated research design and large sample, concerns about statistical power meant that we did not examine moderation by participant age and sex. It would be preferable to examine longitudinal data and include two parents per child, to provide a developmental perspective and explore family interactions. Results should be interpreted in the context of our measures, which reflect participants' own perceptions and are subject to reporter biases, including social desirability bias. Speech samples have been referred to as the 'gold-standard' for assessing parent expressed criticism (e.g., Asarnow et al., 2001), however these data are rarely available with the sample sizes required for genetically-informed research. Whilst researcher-coded assessments could reduce reporter bias, their results are specific to a window of observation, which may not generalise to parents' everyday experiences and perceptions. We note that the parent-offspring association was reduced when using only adolescent reports of internalising, which could reflect bias by shared-method-variance in our main results.

4.5.1. Conclusion

Parental criticism is associated with the development of adolescent internalising problems. We contextualise previous research by testing whether this intergenerational association is attributable to genetic confounding. We show that the association withstands correction for genetic relatedness in our sample, but statistical power was somewhat limited. Literature from child twin, longitudinal and experimental studies all indicate the presence of transactional associations between generations. In sum, parental criticism can be considered part of the environment relevant to the presentation of adolescent internalising symptoms, with adolescent symptoms potentially leading to an increase in parental criticism.

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5. Infant temperament and mothers' symptoms of anxiety and depression: taking a developmental and genetically informed perspective

This chapter is a manuscript that will soon be submitted for peer-review. Supplementary materials for this chapter, as detailed in the text, are included in Appendix D (page 185).

Ahmadzadeh, Y. I., Eilertsen, E. M., Gjerde, L., Cheesman, R., Ystrom, E., Hannigan, L. J.,* McAdams, T. A.* (in prep). Infant temperament and mothers' symptoms of anxiety and depression: taking a developmental and genetically informed perspective.

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5.1. Abstract

Background: Aspects of child temperament are associated with symptoms of anxiety and depression (i.e., internalising) in mothers. Child temperament traits and mothers' internalising symptoms can develop across time and are partially influenced by genetic factors. However, little is known about how they may *co-develop* in families, nor the extent to which mother-child genetic relatedness might explain their association.

Aims: We combined developmental modelling with a genetically informative research design to contribute novel information on co-development and genetic confounding in associations between mothers' internalising symptoms and child temperament across the first five years of life.

Methods: Participants were 34,060 mothers with 42,526 offspring from the Norwegian Mother, Father and Child Cohort Study. Linkage to birth registry data allowed for the identification of extended family structures using this sample. Mothers' internalising symptoms and child temperament (emotionality, activity, shyness and sociability) were measured by maternal report at offspring ages 1.5, 3 and 5 years. Longitudinal models parameterised development of each trait across time, and co-development of traits across generations. A Children-of-Twins/Siblings model was used to control for genetic confounding in any significant cross-time, cross-generation correlations.

Results: Results showed evidence for individual differences in baseline stability and linear change across time for each trait. The only substantive cross-time, cross-trait correlation was found for baseline stability in mothers' internalising symptoms and baseline stability in offspring emotionality (r=.191). Approximately half of this correlation was attributable to genetic relatedness.

Conclusions: We show how developmental methods can be combined with genetically informed designs, to address intergenerational research questions. We found no evidence for the co-development of child temperament and mothers' internalising symptoms. Although baseline levels of child emotionality were weakly associated with mothers' symptom levels, half of this was explained by genetic overlap.

5.2. Introduction

Internalising problems encapsulate common emotional symptoms related to anxiety and depression. They emerge early in life and are known to run in families (Kessler et al., 2007; Kim, Capaldi, Pears, Kerr, & Owen, 2009; Sydsjo, Agnafors, Bladh, & Josefsson, 2018). As such, we see evidence for familial clustering of internalising problems across child development (Connell & Goodman, 2002; Goodman et al., 2011; Lawrence, Murayama, & Creswell, 2018; Micco et al., 2009). In the first years of life, familial risk for internalising is observed in the context of child temperament, in links between mothers' internalising symptoms and a range of child temperament traits (Britton, 2011; Hanington, Ramchandani, & Stein, 2010; Henrichs et al., 2009; McGrath, Records, & Rice, 2008; Melchior et al., 2012; Tees et al., 2010; Tronick & Reck, 2009).

Measures of infant temperament capture individual differences in child reactivity (i.e., responsiveness to change in environments) and self-regulation (i.e., executive control over physiological, affective and behavioural responses; Rothbart & Bates, 2006). Infant temperament can be separated into numerous components, typically relating to individual differences in activity, withdrawal and affect (Rettew & McKee, 2005), which become evident within the first weeks after birth (Rothbart, Chew, & Gartstein, 2001; Zentner & Bates, 2008). Temperament traits are typically measured along continuums, with extreme scores reflecting more 'difficult' temperament (e.g., irregular bodily functions, withdrawal from new situations, slow adaptability, negative mood or intense reactions). Across childhood, extreme temperament scores are associated with higher risk for child psychopathology, including internalising problems, in both cross-sectional and prospective analyses (Abulizi et al., 2017; Goldsmith & Lemery, 2000; Goodyer, Ashby, Altham, Vize, & Cooper, 1993; Martin et al., 2000; Rettew & McKee, 2005).

While associations between infant temperament and parental internalising problems are well-documented, questions remain as to whether these associations are causal. Causal pathways are present if parents' internalising problems directly influence the developmental course of offspring temperament, for example via foetal programming, parenting or social learning (Aktar, Nikolić, & Bögels, 2017; Lieb et al., 2000; O'Connor, Monk, & Fitelson, 2014). Causal effects can also operate in the reverse direction, in line with a transactional model of child development (Sameroff, 2009), if child temperament traits directly influence change in parents' mental health (Kiff, Lengua, & Zalewski, 2011; Moe, von Soest, Fredriksen, Olafsen, & Smith, 2018; Papousek & von Hofacker, 1998). However, genetic relatedness in families may lead to non-causal (i.e., confounded) associations, if the same genes influence both parents' internalising problems and child temperament. This is possible given that all complex traits, including adult internalising problems and child temperament, are influenced in part by genetic factors that tend to have highly diffuse effects (Goldsmith & Lemery, 2000; Nivard et al., 2015; Plomin, DeFries, Knopik, & Neiderhiser, 2016; Saudino et al., 1998). As such, we must consider any effects of genetic confounding in research on familial risk for internalising problems, to establish when and if it is ever reasonable to draw causal inferences from parent-offspring associations.

Genetically informed methods, including adoption, sibling-comparison and extended family designs, can be used to control for genetic confounding in family research. By controlling for the role of genes, these designs enable researchers to approximate the role of any non-genetic, potentially causal influences on parent-offspring associations. Evidence for small, unconfounded associations have been found in several studies examining parent internalising symptoms and offspring temperament traits, using data from a large prospective adoption cohort (Leve et al., 2019). For example, data show evidence for transactional associations between parents' anxiety symptoms and infant negative affect, using parent-infant dyads who are genetically unrelated (Brooker et al., 2015). However, genetically informative research on associations between parent internalising and child temperament in more representative samples is lacking. Research using sibling-comparison and extended family designs exists for associations between parents' internalising and offspring psychopathology symptoms. Here, findings suggest that prospective associations (i.e., maternal symptoms predicting future offspring symptoms) predominately reflect genetic confounding, while concurrent associations (i.e., maternal symptoms predicting offspring symptoms at the same timepoint) reflect both genetic and non-genetic influence (Gjerde et al., 2018; Gjerde et al., 2019; Gjerde et al., 2017). In other words, parent and offspring internalising traits may not exert *lasting* causal influence on one another. However, all of the existing genetically informed studies index developmental phenotypes using single assessments that are fixed in time. They do not consider the possibility of *co-development* between parent and offspring traits.

Whether causal or confounded, parent-child associations are subject to developmental change. Behavioural phenotypes are not fixed and opportunity for change among parents and offspring is pronounced during early child development, in the context of extensive social and physical development. Evidence exists for individual differences in developmental change for internalising symptoms among mothers with young children (Ahmed, Bowen, Feng, & Muhajarine, 2019; Campbell, Matestic, von Stauffenberg, Mohan, & Kirchner, 2007). That is, some mothers may experience an increase in feelings of anxiety or depression after the birth of a child, while others may experience the reverse, or no change at all. While long-term stability in adult internalising problems is predominantly explained by genetic factors, change across time is more influenced by transient environmental factors (Nivard et al., 2015; Torvik et al., 2019). Developmental change in infant temperament is shown to predominate over continuity, with environmental influences explaining variance in change (Partridge & Lerner, 2007; Saudino, Plomin, & DeFries, 1996). Put simply, both mothers' internalising symptoms and child temperament traits can change across time, and the nature of this change in each individual can be attributed in part to their experiences. This means that mothers' internalising symptoms and offspring temperament traits *could* be driving change in one another across time, as a result of environmental exposure between the mother and child. For example, one study has shown that a steeper increase in offspring fearfulness through infancy is associated with more severe symptoms of depression in mothers, although authors did not account for the possibility of genetic confounding (Gartstein et al., 2010).

To our knowledge, developmental pathways have not yet been explored in an intergenerational, genetically informed framework.

Novel research is needed to combine genetically informed intergenerational designs with developmental models, to examine if and how parent and offspring behaviours co-develop. This was the overarching motivation for our study, in the context of understanding associations between mothers' internalising symptoms and offspring temperament traits. Specifically, we sought to understand whether development of mothers' internalising symptoms was associated with development of offspring temperament traits, and whether these associations might reflect causal (non-genetic) pathways between the two. Ultimately, we aim to improve our understanding of how internalising problems cluster within families, by examining longitudinal processes during early child development. First, we used longitudinal structural equation models to explore the development of mother and child traits over time. Second, we combined longitudinal models across generations to explore co-development of the mother and child traits over time. Third, where evidence was found for significant cross-generation co-development, we used an extended family design to quantify and control for the role of genetic confounding in explaining the phenotypic mother-child associations.

5.3. Method

5.3.1. Participants

Data were drawn from the Norwegian Mother, Father and Child Cohort Study (MoBa; Magnus et al., 2016). All pregnant mothers attending a routine ultrasound examination in Norway between 1999 to 2009 were invited to participate. 41% of eligible women were recruited, yielding a total sample of >95,000 mothers, >75,000 fathers and >114,500 children. Current analyses are based on the Intergenerational Transmission of Risk (ITOR) subproject, where MoBa data have been linked with pedigree and zygosity information from the Medical Birth Registry of Norway and the Norwegian Twin Registry. This enables identification of pedigree structures within the MoBa dataset. The current sample is comprised of extended family units, identified via pairs of siblings (twins, full-siblings, or half-siblings) or first cousins in the parent generation. Within each extended family unit, data are used from up to two mothers and up to two children per mother. Some mothers in the MoBa dataset do not have extended family members taking part in the study. These mothers were included in analyses as nuclear family units if they had more than one child in the study. Phenotypic data were drawn from assessments at child ages 1.5, 3 and 5 years, using version 12 of the MoBa quality-assured data files. In total, raw phenotypic data were used for 42,526 offspring born to 34,060 mothers. Not all mothers participated at every age and attrition was evident over time (Ns for each assessment were as follows: 1.5 years = 38,939 children to 31,567 mothers; 3 years = 31,704 children to 25,976 mothers; 5 years = 23,450 children to 20,032 mothers). Table 1 provides an overview of the pedigree structures extracted from registry data for biometric modelling of the phenotypic data.

Table 1. Overview of pedigree structures used for biometric MCoTS analyses

Extended families (N=20,921)		
N stratified by the parent pairs used to identify extended families [a]	***r*A**	**n**
Identical twin pair	1.00	67
Full-sibling or fraternal twin pair	.500	13,147
Maternal/paternal half-sibling pair	.250	754
Cousin pair	.125	6,953
N stratified by mothers' relatedness in each extended family [b]	***r*A**	**n**
Identical twin pair	1.00	48
Full-sibling or fraternal twin pair	.500	4,407
Maternal/paternal half-sibling pair	.250	290
First cousin pair	.125	2,972
Unrelated sisters/cousins-in-law pair	.000	13,204
Number of offspring pairs linked to each mother	***r*A**	**n**
Full-sibling pair	.500	5,579
Maternal half-sibling pair	.250	49
Unpaired (single) offspring	------	23,314
Unpaired nuclear families (N=5,083) [c]		
Number of offspring pairs linked to each mother	***r*A**	**n**
Identical twin pair	1.00	111
Full-sibling or fraternal twin pair	.500	4,951
Maternal half-sibling pair	.250	21

[a] Extended families were identified via adult twin, sibling or cousin pairs enrolled in the MoBa cohort as parents. These included mother-mother, mother-father, or father-father pairs. [b] Phenotypic data were derived from mothers in each extended family. Mothers were genetically unrelated (rA=.000) if their extended family was identified using a mother-father or father-father pair. [c] Mothers who could not be paired into an extended family (i.e., because they did not have a twin, sibling, cousin, sister-in-law, or cousin-in-law in the dataset) were modelled independently in nuclear family units if they had more than one offspring. Mothers who had twin offspring were also modelled independently in nuclear family units. Numbers represent families who had data for at least one individual in our biometric analyses. rA = genetic relatedness coefficient.

5.3.2. Measures

Mothers' internalising symptoms were measured by self-report when children were aged 1.5, 3 and 5 years, using the eight-item version of the short form of the Hopkins Symptom Checklist (SCL-8; Hesbacher, Rickels, Morris, Newman, & Rosenfeld, 1980; Tambs & Røysamb, 2014). Mothers reported on the extent to which they experienced four symptoms relating to anxiety (e.g. nervousness or shakiness) and four symptoms of depression (e.g. feeling hopeless about the future), using a four-point Likert scale ("Not bothered" to "Very bothered"). Mean scores were calculated for each time-point, excluding participants who were missing on more than half of the items. Internal consistency (Cronbach's alpha) was .85, .87 and .86 at each consecutive child age.

Offspring temperament was rated by mothers when children were aged 1.5, 3 and 5 years, using the Emotionality, Activity and Shyness Temperament Questionnaire (EAS; Mathiesen & Tambs,

1999). 12 items were used to assess four child temperament traits: emotionality (e.g. child gets upset or sad easily), activity level (e.g. child is always on the go), shyness (e.g. child takes a long time to warm up to strangers), and sociability (e.g. child finds other people more fun than anything else). Mothers responded using a five-point Likert scale ("Very typical" to "Not at all typical"). Cronbach's alpha for each trait (in order as described above) were as follows: 1.5 years .64/.65/.65/.32, 3 years .64/.64/.66/.51 and 5 years .75/.75/.70/.71. One item indexing child sociability was missing from the 1.5-year assessment. Mean scores for each temperament trait were calculated at each time-point, excluding participants who were missing on more than half of the items. Each trait was scaled such that higher scores indexed a stronger phenotype (i.e., maximum shyness score = maximum shyness; maximum sociability score = maximum sociability).

5.3.3. Analyses

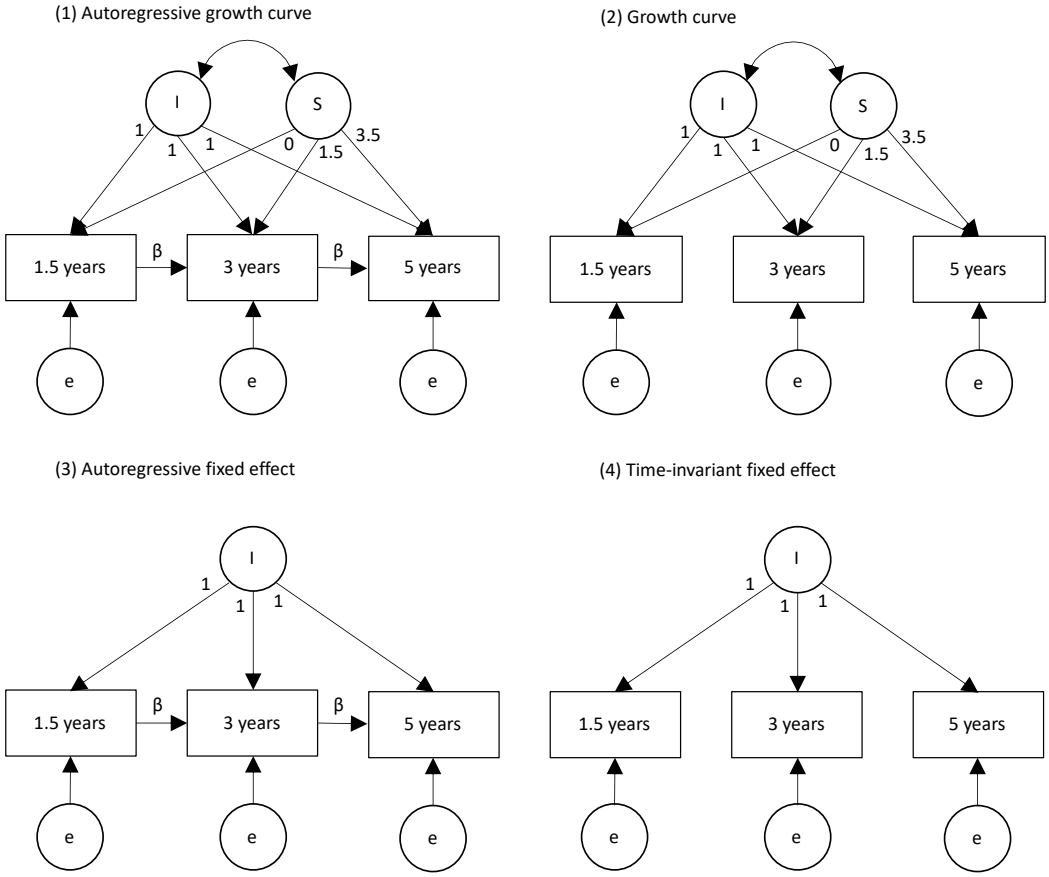
5.3.3.1. Longitudinal modelling of phenotypic data: within-generation

Study variables were regressed on covariates (maternal age, child year of birth, parity, and child sex) and the resultant residuals were standardised. Data for each variable were fitted to longitudinal models (Figure 1), using *lavaan* with Full Information Maximum Likelihood (version 0.6-5; Rosseel, 2012) in R (version 3.4.4), to explore the cross-time covariance structure of each variable. Cluster-robust standard errors were used to account for any effects of structuring of the data in nuclear family units (i.e., non-independence of data points collected from the same mother). If results from robust and classical standard errors diverged then we planned to use multilevel approaches to examine the effects of nested data structures (King & Roberts, 2015).

Autoregressive growth curve models (Bollen & Curran, 2004) were first fitted to the parent and child data separately. Model parameters are depicted in Figure 1 (Model 1). The *latent intercept factor* (I) captured stable variance at the first, baseline assessment (1.5 years), plus any persistent, stable variance shared at 3 and 5 years for each variable. The *latent slope factor* (S) captured variance in the rate at which each variable changed linearly from the first assessment across time (i.e., loading = 0 at 1.5 years). The latent factor means were fixed effects, based on group-level information; while variance around the factor means were random effects, representing within-person information. The *residual error* terms (e) and *autoregressive paths* (β) were modelled to account for additional variance in the observations over time not explained by the intercept or slope factors. These were constrained to be time invariant, to ensure model identification and prevent over-fit. Error terms captured unique variance at each time point while autoregressive paths captured longitudinal prediction of each variable on itself over time, providing an association between the error terms. Autoregressive paths indexed within-person information, since latent factors captured the sample mean structure (Bollen & Curran, 2004; Hamaker, Kuiper, & Grasman, 2015). For example, positive autoregressive paths between two observations would suggest that any participant who scores above their expected value at time

one will be likely to score above their expected value again at time two, as a result of the lagged effects of the first observation. In sum, the autoregressive growth curve model indexes both fixed and random effects of baseline stability and rate of linear change in each variable, whilst accounting for within-person lagged effects of the repeated measures across time.

Figure 1. Within-generation models fitted to the longitudinal data, for each study variable



Models used to explore trait cross-time covariance structure. Models 2 – 4 are nested in Model 1. Rectangles denote measured variables. Circles denote latent factors. One-headed arrows denote regression paths. Double-headed arrows denote correlations. I = intercept (capturing time-invariant variance); e = residual error (capturing time-variant variance, set to be equal across observations for each variable); S = slope (capturing linear change across observations from 1.5 years); β = autoregressive paths (capturing within-person, longitudinal prediction of each variable on itself).

Next, to test the significance of model parameters, the autoregressive growth curve model was constrained to produce three nested models. Dropping autoregressive paths resulted in a growth curve model (Figure 1, Model 2). Dropping the latent slope factor resulted in an autoregressive

fixed effect model (Figure 1, Model 3). Dropping both the autoregressive paths and latent slope factor resulted in a time-invariant fixed effect model (Figure 1, Model 4). Model 4 indicates a purely stable, persistent structure of the data across time, with shared variance at each observation captured in a single common factor. Chi square goodness of fit tests were used to statistically compare the fit of Models 2 – 4 to that of Model 1. If more than one of the nested models were found to provide a better fit compared to Model 1, then these were compared using further Chi square tests (i.e., if nested within one another: as for Model 4 in 2 or 3) or by visual inspection of the fit statistics (i.e., if not nested within one another: as for Models 2 and 3). The best fitting model for each variable was taken forward for inclusion in cross-generation longitudinal models.

5.3.3.2. Longitudinal modelling of phenotypic data: cross-generation

Cross-generation models combined the best fitting model for maternal internalising with the best fitting model for each child temperament trait. All latent factors were allowed to correlate in each cross-generation model. Nested model fit was tested by systematically dropping each intergenerational latent factor correlation. Those that could not be dropped without compromising model fit indexed significant cross-time intergenerational covariance. Within-person latent factor scores were extracted for each individual in the sample. These were taken forward for biometric modelling, to examine genetic versus environmental pathways underpinning any significant intergenerational associations.

5.3.3.3. Extended family design: decomposing intergenerational covariance

Biometric models, using a Multiple-Children-of-Twins/Siblings (MCoTS; McAdams et al., 2018) extended family design (see full path diagram in Figure S1, Appendix D), were fitted for significant intergenerational latent factor correlations, using *OpenMx* (version 2.12.1; Neale et al., 2016) in R (version 3.4.4). We ran biometric analyses only for intergenerational latent factor correlations where $r>.10$, given that covariance decompositions are likely to be less informative for weak associations (demands on statistical power are higher for decomposing lower parent-offspring correlations; see analyses in Chapter 4 of this thesis).

The MCoTS design makes use of data from adult parents and their offspring in extended families. The genetic correlation between all parents and offspring is .50, because offspring inherit half of their DNA from each of their parents. As depicted in Figure 2, when identical twins have children, their offspring will be just as genetically related to their own parent compared to their parent's twin (genetic correlation = .50). When fraternal twins or full-siblings have children, their offspring will be more genetically related to their own parent than their parent's twin or sibling (genetic correlation = .25). Accordingly, the offspring of half-siblings and cousins will be more genetically related to their own parent than to their parent's half-sibling or cousin (see Figure 2). Alongside genetic relatedness estimates, it is assumed in extended family designs that all children share their immediate rearing environment only with their parent, not with their parent's twin, sibling, half-sibling or cousin. This provides a natural experiment whereby phenotypic correlations

between children and their parent's twin, sibling, half-sibling or cousin (referred to as 'avuncular' associations)[1] can be used to estimate the effect of genetic relatedness on intergenerational associations. In other words, if avuncular associations are stronger in extended families who are more genetically related, this indicates a role of shared genetic effects acting across generations. By controlling for the role of genetic relatedness on intergenerational associations, it becomes possible to estimate the influence of pathways in the child's immediate rearing environment, above and beyond what is attributable to genetic transmission.

Figure 2. Genetic relatedness estimates used in extended family designs

Brackets show the genetic correlation (rA) between each relative and the index case. The spouse of each relative can also be included in extended family designs. Spouses would have a genetic correlation of .00 with the index case (i.e., assuming that the index case is not genetically related to any spouse of their siblings or cousins).

In practise, MCoTS analyses are an extension of the traditional twin design (Plomin, DeFries, & Knopik, 2012). In the traditional twin design, population variance for any trait of interest is decomposed into three latent factors labelled A, C and E. The A factor captures trait heritability, representing the proportion of population variance that is attributable to genetic variation in a given sample (i.e., additive genetic effects). The C factor captures the proportion of population variance that is attributable to environments shared between related individuals (i.e., common environmental effects). The E factor captures the proportion of population variance that is attributable to environments that are unique to each individual (i.e., unique environmental effects), plus measurement error. In MCoTS models we decompose variance in both a parent and child trait, as well as covariance between these traits (full model specification is provided in Figure S1, Appendix D). This provides three sets of information, outlined below in the context of this study.

First, data from pairs of differentially related mothers (i.e., MZ twins, DZ twins, full- and half-siblings, cousins, and unrelated sisters/cousins-in-law) were used to decompose variance in

[1] The term 'avuncular' relates to the relationship between individuals and the children of their siblings. For simplicity in this manuscript, we use this term to also include the relationship between individuals and the children of their cousins.

mothers' internalising into additive genetic (A1), common environmental (C1), and unique environmental (E1) components. Second, data from differentially related children (i.e., MZ twins, DZ twins, full-siblings, maternal-half-siblings, and cousins) were used to decompose variance in child emotionality into equivalent genetic and environmental components (A2, C2, and E2). Third, data from differentially related avuncular pairs were used to decompose covariance between generations into three paths: effects of genetic transmission (a1'; accounting for the effects of genes shared between generations); effects of the extended family environment (c1'; accounting for the effects of environments that are shared between all members of an extended family);[2] and residual phenotypic transmission (*p*; accounting for all non-genetic effects shared between the parent and child, plus the effects of any sources of confounding that remained unaccounted for).

5.4. Results

5.4.1. Descriptive statistics

Descriptive statistics for the raw study data are shown in Table S1 (Appendix D). Total scores for mothers' internalising symptoms were low on average, showing positively skewed distributions. Child temperament scores were moderate and normally distributed on average. Phenotypic, cross-sectional correlations between all study variables were weak or negligible, as shown in Table S2 (Appendix D).

5.4.2. Longitudinal modelling of phenotypic data: within-generation

The autoregressive growth-curve model (Model 1) fit the longitudinal data well for maternal internalising and all measures of child temperament (Table 2). Neither the latent slope factor nor autoregressive paths could be dropped without compromising model fit, for any variable (Table 3). Parameter estimates are shown in Table 4. Variance in baseline stability (latent intercept factors, I) was significant and substantial for all variables, indicating individual differences in participants' trait scores at 1.5 years (.279 – .554). Variance in the rate of linear change (latent slope factors, S) was low, suggesting high levels of homogeneity in individuals' longitudinal rate of change (.005 – .018). Slope factor *variance* was not significant for offspring sociability (Table 4) and this variance could be fixed to zero without compromising model fit (Table S3, Appendix D; NB the slope factor could not be dropped completely [Table 3], suggesting evidence for linear change across time, but no individual-level variability in rate of change for sociability). Weak, negative correlations were found between latent intercept and slope factors for each variable. These suggested that participants who started with higher trait scores were more likely to decrease at a greater rate across time, and vice versa (r = -.041 – -.013), in line with 'regression

[2] Our definition of the extended family environment (c1') applies to extended families linked by mothers who are twins, full-siblings or maternal half-siblings. We expect these mothers to have been reared together in the same environment (rC=1). We expect that mothers in extended families who are paternal half-siblings, cousins or unrelated sisters/cousins-in-law will not have been reared together in the same environment (rC=0), therefore these families do not share an extended family environment.

towards the mean' (Bland & Altman, 1994). Residual error terms showed evidence for moderate heterogeneity between observations for each variable (e = .460 – .697). Significant autoregressive effects (β = .068 – .113) showed lagged effects of trait observations across time for all variables (i.e., it was necessary to include autoregressive paths to account for significant associations between the residual error terms).

Table 2. Model fit statistics for within- and cross-generation autoregressive growth-curve models

	CFI	TLI	RMSEA (95% CI)	RMSEA p
Within-generation				
Child Emotionality	.998	.998	.015 (.001, .021)	1.00
Child Activity	.993	.989	.039 (.034, .045)	.999
Child Shyness	.986	.979	.050 (.045, .056)	.454
Child Sociability	.983	.974	.041 (.035, .047)	.996
Mother Internalising	.998	.998	.019 (.013, .025)	1.00
Cross-generation				
Child Emotionality – Mother Internalising	.998	.996	.014 (.012, .017)	1.00
Child Activity – Mother Internalising	.995	.992	.020 (.018, .023)	1.00
Child Shyness – Mother Internalising	.993	.988	.025 (.023, .028)	1.00
Child Sociability – Mother Internalising	.994	.989	.021 (.018, .024)	1.00

Table 3. Chi square goodness of fit tests for longitudinal modelling of phenotypic, within-generation data

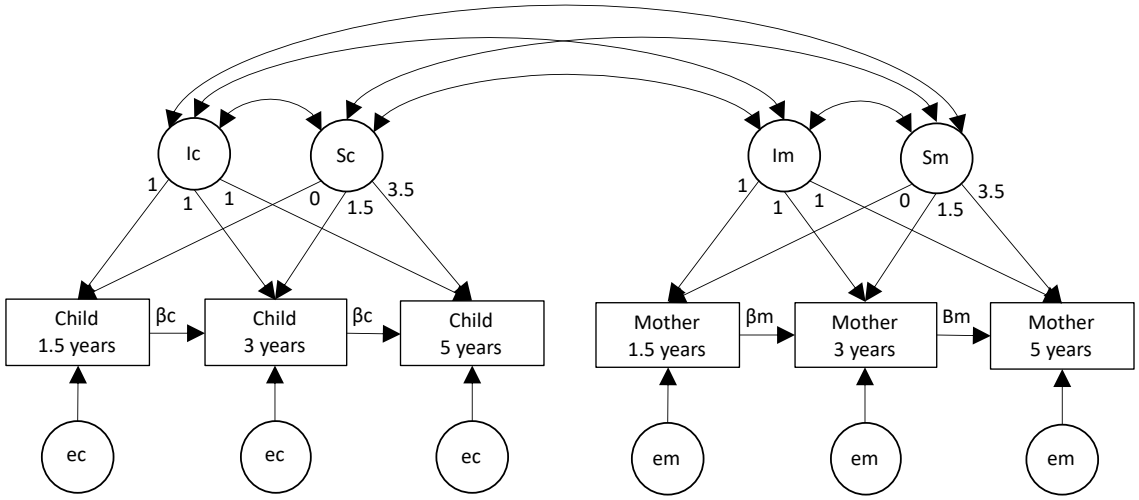
Model	df	AIC	BIC	Chi^2	ΔChi^2	Δdf	p
Child Emotionality							
1. Autoregressive growth curve	2	252557.7	252618.3	21.818	--	--	--
2. Growth curve	3	252642.0	252693.9	108.072	85.704	1	<.0001
3. Autoregressive fixed effect	5	252735.4	252770.0	250.480	181.996	3	<.0001
4. Time-invariant fixed effect	6	252997.6	253023.6	469.669	437.854	4	<.0001
Child Activity							
1. Autoregressive growth curve	2	248670.5	248731.1	131.481	--	--	--
2. Growth curve	3	248777.6	248829.5	240.578	109.097	1	<.0001
3. Autoregressive fixed effect	5	248962.7	248997.3	429.711	298.230	3	<.0001
4. Time-invariant fixed effect	6	249374.9	249400.9	843.963	712.482	4	<.0001
Child Shyness							
1. Autoregressive growth curve	2	250328.9	250389.5	216.649	--	--	--
2. Growth curve	3	250432.1	250484.1	321.8668	105.218	1	<.0001
3. Autoregressive fixed effect	5	250515.4	250550.0	409.108	192.459	3	<.0001
4. Time-invariant fixed effect	6	250931.8	250957.7	827.491	610.842	4	<.0001
Child Sociability							
1. Autoregressive growth curve	2	257925.3	257985.9	143.009	--	--	--
2. Growth curve	3	257999.0	258050.9	218.6875	75.678	1	<.0001
3. Autoregressive fixed effect	5	257941.5	257976.1	165.233	22.224	3	.0002
4. Time-invariant fixed effect	6	258182.2	258208.2	407.950	264.941	4	<.0001
Mother Internalising							
1. Autoregressive growth curve	2	241579.4	241639.9	30.929	--	--	--
2. Growth curve	3	241631.8	241683.7	85.355	54.427	1	<.0001
3. Autoregressive fixed effect	5	241764.1	241798.7	221.645	190.716	3	<.0001
4. Time-invariant fixed effect	6	241869.4	241895.3	328.901	297.972	4	<.0001

Table 4. Parameter estimates in each within-generation autoregressive growth-curve model

	Variance in baseline stability: I	Variance in rate of linear change: S	Correlation (*r*): I – S	Autoregressive effects: β	Residual error: e
Child Emotionality	.434 (.408, .460)	.014 (.011, .017)	-.035 (-.040, -.029)	.097 (.075, .119)	.559 (.540, .578)
Child Activity	.492 (.468, .516)	.018 (.015, .021)	-.041 (-.046, -.037)	.106 (.085, .128)	.493 (.477, .509)
Child Shyness	.449 (.422, .475)	.015 (.012, .018)	-.035 (-.040, -.030)	.113 (.090, .137)	.530 (.511, .548)
Child Sociability	.279 (.245, .313)	.005 (-.000, .009)	-.013 (-.019, -.006)	.112 (.085, .140)	.697 (.670, .724)
Mother Internalising	.554 (.533, .575)	.012 (.009, .014)	-.032 (-.036, -.027)	.068 (.049, .087)	.460 (.447, .472)

Results from analyses using classical standard errors did not diverge from results using cluster-robust standard errors (presented results use the latter), thereby suggesting no effect of the nested data structure (i.e., nesting of mother-child dyads into nuclear families) on model parameters. For each variable, the autoregressive growth-curve model was carried forwards for inclusion in cross-generation longitudinal models.

Figure 3. Cross-generation autoregressive growth curve model



Model used to explore cross-generation, cross-time covariance structure of mother and child traits. Rectangles denote measured variables. Circles denote latent factors. One-headed arrows denote regression paths. Double-headed arrows denote correlations. I = intercept (capturing time-invariant variance); e = residual error (capturing time-variant variance, set to be equal across observations for each variable); S = slope (capturing linear change across observations from 1.5 years); β = autoregressive paths (capturing within-person, longitudinal prediction of each variable on itself).

Table 5. Correlation matrix for latent factors in each cross-generation autoregressive growth-curve model

		Child Temperament		Mother Internalising	
		1. Baseline stability (Ic)	2. Rate of linear change (Sc)	3. Baseline stability (Im)	4. Rate of linear change (Sm)
Emotionality	1.	--			
	2.	-.034 (-.041, -.028)	--		
	3.	**.143 (.130, .156)**	-.004 (-.010, .001)	--	
	4.	**-.016 (-.004, -.011)**	**.007 (.005, .009)**	-.032 (-.043, -.021)	--
Activity	1.	--			
	2.	-.041 (-.048, -.035)	--		
	3.	**-.015 (-.027, -.002)**	**.007 (.002, .012)**	--	
	4.	.004 (-.001, .008)	-.000 (-.002, .001)	-.032 (-.043, -.021)	--
Shyness	1.	--			
	2.	-.035 (-.042, -.028)	--		
	3.	**.031 (.019, .044)**	.002 (-.004, .007)	--	
	4.	-.004 *(-.008, .001)	**.002 (.000, .004)**	-.032 (-.043, -.021)	--
Sociability	1.	--			
	2.	-.013 (-.023, -.003)	--		
	3.	**-.015 (-.028, -.003)**	-.003 (-.008, .003)	--	
	4.	-.000 (-.005, .004)	-.001 (-.003, .001)	-.032 (-.043, -.021)	--

White boxes = within-generation latent factor correlations. Grey boxes = cross-generation latent factor correlations. Bold = parameters that could not be dropped from the model without significant detriment to model fit. Confidence intervals are Bonferroni adjusted to account for four multiple tests with mother internalising (CI = 98.75%). One parameter became non-significant after Bonferroni adjustment (*).

5.4.3. Longitudinal modelling of phenotypic data: cross-generation

Figure 3 shows the model specification for cross-generation autoregressive growth-curve models, conducted for mothers' internalising symptoms and each child temperament trait. This model fit the data well for all variable combinations (Table 2). Table 5 shows the parameter estimates for the intergenerational latent factor correlations in each model. Bonferroni correction was used to adjust confidence intervals, to account for multiple testing (i.e., intergenerational associations with mothers' internalising problems were examined four times, using each offspring temperament trait, so confidence intervals were corrected to 98.75% [1-(0.05/4)]). All cross-generation latent factor correlations were low (grey boxes) and half were significant (grey boxes, bold text). Nested

models confirmed that only the non-significant correlations could be dropped without compromising model fit (Table S4, Appendix D). The greatest correlation was found between baseline stability in mothers' internalising symptoms and offspring temperament (*r*=.143). All other cross-generation correlations between latent intercept factors were below .100. These mirrored cross-sectional phenotypic correlations in our data at 1.5 years (Table S2, Appendix D). All intergenerational correlations involving rate of linear change in mother and/or child traits were negligible. As such, results did not provide evidence for any substantive co-development of mothers' internalising symptoms with any of the child temperament traits across time.

Again, model results from cross-generation analyses using classical standard errors did not diverge from results using cluster-robust standard errors, thereby suggesting no effect of the nested data structure on results. Latent intercept factor scores for child emotionality and mothers' internalising symptoms were the only variables taken forward for biometric modelling. These were extracted from the within-generation autoregressive growth curve models. Extracted factor scores from within-generation models showed a pairwise correlation of .191.

5.4.4. Extended family design: decomposing intergenerational covariance

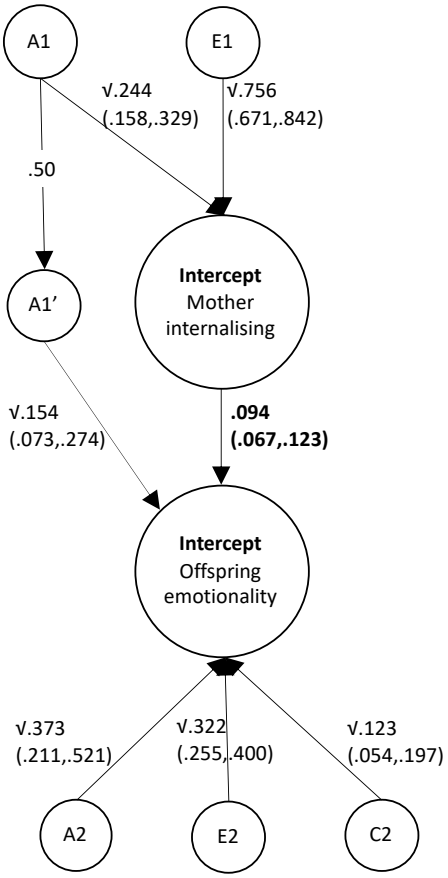
Decomposition of variance in baseline stability for child emotionality and mothers' internalising symptoms, and the covariance between them, was conducted using the MCoTS extended family design. Parameter estimates for the base model are shown in Figure S2 (Appendix D). Estimates for C1 (indexing variance explained in mothers' internalising by shared environmental factors in a mother pair) and c1' (indexing intergenerational covariance explained by shared environmental factors in the extended family) were not significantly different from zero, so were dropped from the model. This resulted in a more parsimonious model without detriment to model fit (Table S5, Appendix D), thereby increasing statistical power for the estimation of remaining parameters.

As shown in Figure 4, 22.4% (A1; CI 15.8 – 32.9%) of the variance in baseline stability for mothers' internalising symptoms could be explained by genetic factors in the parent generation. 37.3% (A2; CI 21.1 – 52.1%) of the variance in baseline stability for child emotionality could be explained by genetic factors unique to the child generation, while 15.4% (A1', CI 7.3 – 27.4%) could be explained by shared genetic factors in the child generation that were *also acting in the parent generation* to influence mothers' internalising. As such, child emotionality was 52.7% heritable.

After accounting for intergenerational covariance explained by genetic factors (A1'), the residual intergenerational causal path was significant (.094, CI .067 - .123). Put another way, 50.7% (CI 36.1 – 64.6%) of the phenotypic correlation between baseline stability for child emotionality and baseline stability for mothers' internalising symptoms (*r*=.191) was explained by genetic factors common to each, while the remaining 49.3% (CI 35.4 – 63.9%) could be explained by residual

phenotypic (i.e., non-genetic) effects.[3] Both contributions were significant. Neither A1' nor p could be dropped without significant deterioration in model fit (Table S5, Appendix D).

Figure 4. Results from MCoTS biometric analyses, decomposing the association between baseline stability in mothers' internalising symptoms and baseline stability in offspring emotionality (*r* = .191)



A1 = additive genetic effects on mother trait; A2 = additive genetic effects specific to offspring trait; A1′ = additive genetic effects common to mother and offspring traits (path from A1 to A1′ is fixed to .50 because offspring inherit 50% of their mother's genes); C2 = common environment effects on offspring trait; E1/E2 = unique environment effects on mother/offspring trait. Variance components are displayed in non-bold text. The residual intergenerational association is displayed as a standardised path beta coefficient in bold text. Figure represents a partial path diagram.

[3] The relative contribution of A1' in explaining the parent-child correlation is calculated by multiplying the genetic paths connecting each trait, divided by the total phenotypic correlation: ((√.224*.50*√.154)/.191)

5.5. Discussion

We present novel research combining developmental models with genetically informed, intergenerational methods, to examine if and how maternal internalising symptoms and child temperament traits co-develop in the first five years of life. First, we parameterised development of mothers' internalising symptoms and offspring temperament traits between child ages 1.5 – 5 years. We found evidence for individual differences in baseline stability and linear change across time. Second, we explored the co-development of variables across generations. The only substantial cross-generation covariance found was that between latent factors indexing baseline stability in mothers' internalising symptoms and baseline stability in offspring emotionality. This demonstrated a positive, intergenerational association between baseline trait *levels*, but not between trait *change*. Finally, when we decomposed this significant correlation, around half of the association was attributable to genetic confounding. That is, stable baseline variance in mothers' internalising symptoms was influenced in part by genetic factors, which were in part the same genetic factors influencing stable baseline variance in offspring emotionality. The remainder of the intergenerational covariance was attributable to non-genetic influences, which could include causal influences between the parent and child, in either direction.

5.5.1. Intergenerational correlations: mothers' internalising symptoms showed stronger correlations with offspring emotionality compared to activity, shyness and sociability

Our observed correlation between baseline stability in mothers' internalising symptoms and baseline stability in offspring emotionality matched results reported in previous studies examining child emotionality (e.g., Britton, 2011; McGrath et al., 2008; Tronick & Reck, 2009), as well as the cross-sectional correlations observed in our data at each timepoint (Table S1, Appendix D). Together, these results support the notion that mothers who self-report higher levels of internalising symptoms are more likely to report higher, concurrent levels of emotionality among infant offspring. We used a large sample with unprecedented statistical power for precisely estimating intergenerational correlations. However, we found only very small correlations between measures of mothers' internalising symptoms and offspring activity, shyness and sociability – both within and across time. This was surprising for the measure of shyness in particular, since previous research suggests that child shyness is predictive of child emotional problems (Abulizi et al., 2017). Our findings contrasted with previous research showing larger, significant associations involving a range of child temperament traits, including measures of child activity, affect, adaptability and approach (e.g., Britton, 2011; Henrichs et al., 2009; Tees et al., 2010). This could be reflective of publication bias within existing literature, whereby researchers and journals are more likely to seek publication for significant results. As such, we begin by emphasising the importance of our results in highlighting aspects of child development that did not appear to be related to mothers' internalising symptoms in our large sample, and therefore may not be useful markers for the early detection of familial risk for internalising problems.

5.5.2. Baseline stability: the association between mothers' internalising symptoms and offspring emotionality was confounded by their genetic relatedness

We use an extended family design to show that approximately half of the stable, baseline association between mothers' internalising symptoms and offspring emotionality could be attributed to their genetic relatedness. This means that the same genes act as a common cause, to some degree, for the stable components of both mothers' internalising symptoms and offspring emotionality. To our knowledge, this is the first study demonstrate genetic overlap between adult internalising symptoms and early child temperament. After accounting for genetic overlap, we found a reduced, albeit significant, residual association that was attributable to non-genetic influences on parent-child covariance (standardised $\beta = .094$). Genetic overlap has previously been reported for associations involving mothers' internalising symptoms and offspring psychopathology during early childhood, in the same sample as in this study (Gjerde et al., 2018; Gjerde et al., 2019; Gjerde et al., 2017). Together we show that associations between parent internalising and child emotional problems should be considered partially confounded by their genetic relatedness.

5.5.3. Rate of change: no evidence was found for the co-development of mothers' internalising symptoms and offspring temperament traits

Ours is the first genetically informed study to explore the ways in which parent-offspring correlations might develop across time. Although genetic factors are known to influence longitudinal stability in adult internalising symptoms and child temperament, evidence suggests that *change* may be more environmentally driven (Hannigan, Walaker, Waszczuk, McAdams, & Eley, 2016; Nivard et al., 2015; Saudino et al., 1996; Torvik et al., 2019). Through developmental modelling we showed evidence for significant linear change in mothers' internalising symptoms and offspring temperament traits across time. Variance, or individual differences, in the rate of linear change was significant for all variables, except offspring sociability. However, substantive evidence was not found for the co-development of mother and child variables. Although parameters of change in the parent and child generation were significantly correlated in some instances (Table 5), these correlations were extremely small and it is difficult to imagine how these could be extrapolated to tangible processes in 'real-life' (very weak correlations were statistically significant as a result of our large sample size). Therefore, we conclude that evidence was not sufficient to support the notion that change in mothers' internalising symptoms predicts change in offspring temperament traits across time, and vice versa.

Our results support previous, genetically-informative research in suggesting that parent and offspring internalising traits may not exert *lasting* causal influence on one another across time (Gjerde et al., 2018; Gjerde et al., 2017). It could be that these studies, including our own, have been conducted across timeframes that are temporally too wide to detect causal influences between generations. Conducting repeat data collections across shorter timeframes is a

challenge when working with the sample sizes required for genetically informed research. Further, results may differ within samples where parents experience more severe internalising symptoms and/or offspring show more difficult temperament. Exposure to clinically relevant mental health problems in parents or offspring might have more tangible, lasting effects on development among family members.

5.5.4. Opportunities to expand on our methods in future research

Structural equation modelling provides a flexible framework to statistically represent and test complex theories (Bollen & Pearl, 2013). We show how researchers can start to combine developmental and intergenerational transmission models, to scrutinise the processes that underpin familial risk for mental health problems. While parallel research efforts in both domains have shown the importance of considering how phenotypes change across time and the contribution of genetic factors in families, we emphasise that these now need to come together. In this study we parametrise population variance across time in terms of linear change. Although we found significant evidence for linear change in our sample, it is possible that quadratic growth terms would fit the data better. We did not have sufficient degrees of freedom to model these. Alternative model specifications could be explored next, ideally with phenotypes that show stronger intergenerational correlations. New models could include (and correlate intergenerationally) random effects for the autoregressive paths, to examine how instability in maternal mental health impacts, or is impacted by, child behaviour. Moving forwards it will be important to consider whether autoregressive growth-curve models provide the best fit in this study because they provide the best explanation for our data, or whether they fit best because they are the largest models (i.e., the least parsimonious) with highest tendency to fit *any data* better (i.e., highest fit propensity; Falk & Muthukrishna, 2020). It was promising to find that Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) results provided support for use of the autoregressive growth-curve models in our analyses, even though both methods are designed to favour model parsimony (the BIC method uses a stricter penalty term for the number of parameters in the model compared to the AIC method; Schwarz, 1978). It is a challenge when using structural equation modelling to strike the right balance between expanding models to fit true patterns in the data versus maintaining parsimony to avoid also fitting spurious patterns. For any developmental models used in future research, it will also be possible to model latent factor scores within different genetically informed designs, including adoption and sibling-comparison research. As such, opportunities for further research using a range of methods and samples are rich and will be important for replicating and scrutinising findings.

5.5.5. Study limitations

Some final limitations warrant emphasis. First, all phenotypes were reported by mothers. Data collection from multiple reporters is logistically and financially difficult in such large samples and mothers are arguably best placed to inform on behaviours in their young offspring. However,

phenotypic, intergenerational correlations may have been inflated by shared method variance, for example if mothers experiencing higher levels of internalising symptoms perceived higher emotionality in their infant. We suggest that if shared method variance had affected our results, it would have led to underestimation of the genetic contribution to intergenerational associations, since parent-child correlations would be inflated over-and-above avuncular correlations. Second, we found that our measure of mothers' internalising symptoms was positively skewed, reflecting low levels of reported impairment. Others have shown that, on average, participating mothers in the MoBa experience lower levels of mental impairment compared to those who did not volunteer to participate from the Norwegian population, and those who were lost to the study through attrition (Nilsen et al., 2009). However, these authors suggest that low prevalence rates do not necessarily lead to biases in estimates of associations between exposures and outcomes. Linkage to Norwegian medical registries could help somewhat to identify families experiencing clinically relevant symptoms in future research. This would not provide a complete solution given that most individuals do not seek professional help for internalising symptoms and are therefore not recorded in registry data (Roness, Mykletun, & Dahl, 2005). As discussed above, analyses could be improved by use of more frequent longitudinal assessments, shedding light on how parents and offspring change within years, in addition to between years. Longer, more detailed measures may also help to identify sources of parent-offspring similarity. Finally, it would be preferable to also examine the influence of fathers in this research effort. As in all research, we urge caution in extrapolating our findings to different populations, for example those with different levels of impairment, child age or parent sex.

5.5.6. Conclusion

This study is strengthened by the use of sophisticated developmental and genetically informed research designs in a large sample. Results show that baseline stability in mothers' internalising symptoms is associated with baseline stability in offspring emotionality during early development, in part as a result of their genetic relatedness. Although mothers' internalising symptoms and offspring emotionality changed significantly across the observed 3.5-year period, we found no substantial evidence for their co-development across time. Further, we found no cross-time, cross-generation associations with offspring activity level, sociability, nor shyness. Researchers should strive to conduct new genetically informed, intergenerational research within a developmental framework, building on our proposed methodology to explore familial risk for psychopathology. Extensive further research is warranted before results can be extrapolated to inform clinical practise.

5.6. References

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6. Children of the Twins Early Development Study (CoTEDS): a Children-of-Twins study

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Article

Children of the Twins Early Development Study (CoTEDS): A Children-of-Twins Study

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Abstract

The Children of the Twins Early Development Study (CoTEDS) is a new prospective children-of-twins study in the UK, designed to investigate intergenerational associations across child developmental stages. CoTEDS will enable research on genetic and environmental factors that underpin parent–child associations, with a focus on mental health and cognitive-related traits. Through CoTEDS, we will have a new lens to examine the roles that parents play in influencing child development, as well as the genetic and environmental factors that shape parenting behavior and experiences. Recruitment is ongoing from the sample of approximately 20,000 contactable adult twins who have been enrolled in the Twins Early Development Study (TEDS) since infancy. TEDS twins are invited to register all offspring to CoTEDS at birth, with 554 children registered as of May 2019. By recruiting the second generation of TEDS participants, CoTEDS will include information on adult twins and their offspring from infancy. Parent questionnaire-based data collection is now underway for 1- and 2-year-old CoTEDS infants, with further waves of data collection planned. Current data collection includes the following primary constructs: child mental health, temperament, language and cognitive development; parent mental health and social relationships; parenting behaviors and feelings; and other socioecological factors. Measurement tools have been selected with reference to existing genetically informative cohort studies to ensure overlap in phenotypes measured at corresponding stages of development. This built-in study overlap is intended to enable replication and triangulation of future analyses across samples and research designs. Here, we summarize study protocols and measurement procedures and describe future plans.

Keywords: Behavioral genetics; children-of-twins; families; longitudinal; offspring; parents

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To date, most genetically informative research examining the origin of human traits has relied on twin studies to derive heritability estimates and related statistics (e.g. Polderman et al., 2015). Twin studies are based on comparisons of monozygotic (MZ) and dizygotic (DZ) twins to decompose the etiology of individual differences into genetic, shared environment and nonshared environment components. In this way, twin studies are focused on identifying etiological influences that make twins in the same generation more similar or different to one another. While twin heritability estimates go some way toward explaining why traits run in families, within-generation studies miss some of the picture — because it is also of interest to understand the factors underlying correlations between generations.

Parents and children are similar to one another, to a degree, in almost all measurable traits. These include physical characteristics (e.g. Jaaskelainen et al., 2011), personality traits (e.g. Boutwell & Beaver, 2010), psychopathology (e.g. Micco et al., 2009), cognitive ability (e.g. Bouchard & McGue, 1981), educational attainment (e.g. Hertz et al., 2007) and observed behaviors, such as cigarette smoking (Chassin et al., 2008). Cross-trait correlations are also found between generations, for example, between parent substance use and child psychopathology (Vidal et al., 2012). Such parent–child associations may arise through one or more of the following possible mechanisms: (1) Parents may have a direct effect on their children, influencing offspring development in some way through their behavior. For example, parental affection may increase feelings of self-worth in their children (McAdams et al., 2017). (2) Children may inherit genetic variants associated with the parent and child traits of interest. For example, genetic factors associated with depression in parents have been found to manifest as conduct problems in adolescent offspring, partially accounting for the phenotypic association between the parent and child traits (Silberg et al., 2010). This is an example of passive gene–environment correlation, whereby the child's genotype is correlated with the environment in which they are reared (with their environment characterized by the parent's genetically influenced trait of interest; Plomin et al., 1977). Accounting for passive gene–environment correlation is of crucial importance in distinguishing possible causal effects of parent–child interactions from the effects of genetic relatedness. (3) Parents and children share their environments at various levels. They inhabit the same or overlapping

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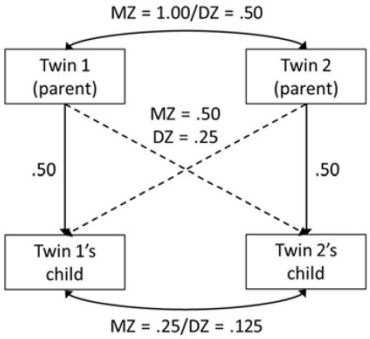

Fig. 1. Genetic correlations for monozygotic (MZ) and dizygotic (DZ) twin-pairs and their children.[a]
Note: [a]Dashed lines show avuncular associations.

cultures, neighborhoods, extended families and nuclear families. Environmental influences operating at one or more of these levels can increase or induce correlations between parent and child traits. (4) Children may have a direct effect on their parents. For example, child anxiety symptoms can prospectively predict future anxiety symptoms in mothers (Ahmadzadeh et al., 2019); and children may influence the parenting that they receive (Avinun & Knafo, 2014; Oliver et al., 2014).

While studies of twins and their parents can be useful in understanding the nature of associations between parent and child traits, they can only ever tell us about the role of offspring genes in these associations because we only have information on the relatedness between people within the offspring generation (the twins' generation). In the *children-of-twins* (CoT) design, it is possible to explore the effects of parents on children, and vice versa, while accounting for the potential confounding effects of parent *and* child genes (and thus passive gene–environment correlation) and shared family environments.

The CoT design involves studying samples of twins and their children (D'Onofrio et al., 2003; Fischer, 2018; Heath et al., 1985; McAdams et al., 2014, 2018; Nance & Corey, 1976; Silberg et al., 2010). Children inherit 50% of their DNA from each of their parents. As depicted in Figure 1, because MZ twins share all of their segregating genes, when both twins in an MZ twin-pair have children, their offspring are just as genetically related to their own parent (genetic correlation = .50) as they are to their parent's genetically identical twin (avuncular genetic correlation = .50). In contrast, because DZ twins share 50% of their segregating genes on average, when both twins in a DZ twin-pair have children, their offspring are more genetically related to their own parent (genetic correlation = .50) than they are to their parent's non-identical twin (avuncular genetic correlation = .25). Subsequently, cousins who are offspring of MZ twins are more genetically related to each other (genetic correlation = .25) compared to the offspring of DZ twins (genetic correlation = .125). Comparisons between avuncular correlations in these extended families linked by MZ versus DZ twin parents thus provide researchers with a natural, quasi-experiment for the study of associations between parent and child phenotypes.

Here, we describe the procedural and measurement aspects of the first British CoT sample, the Children of the Twins Early Development Study (CoTEDS). CoTEDS is a spin-off from the Twins Early Development Study (TEDS; Rimfeld et al., 2019). The TEDS sample includes approximately 10,000 contactable twin-pairs who have been followed longitudinally from infancy through adulthood. At the time of writing, TEDS twins were aged 22–25 years old. The zygosity of TEDS twins was assigned using a parent-reported questionnaire of physical similarity, which is found to be over 95% accurate (Price et al., 2000), and DNA testing was undertaken where zygosity remained unclear (the current sample includes 64% DZ, 33% MZ and 3% unknown). As TEDS twins begin to have children of their own, they are invited to join CoTEDS with their offspring. In the initial stages, CoTEDS has been designed to partially mirror the early years of TEDS data collection, to create a two-generation dataset that includes many of the same phenotypic measures on parents and offspring at corresponding stages of early development. New phenotypes are also being assessed in CoTEDS, relating specifically to parent and offspring mental health, as well as parenting behaviors and feelings.

Research Aims

CoTEDS has been designed to address several types of research questions. Our primary aim is to use the two-generation, longitudinal dataset to understand genetic and environmental factors that underpin intergenerational transmission of common traits within families, with a specific focus on the transmission of cognitive and mental health-related phenotypes. Our secondary aim is to understand the degree to which parenting affects child development and vice versa. Third, in TEDS adults, we aim to examine the genetic and environmental factors that influence individuals' experiences and behaviors during parenthood.

From the outset, CoTEDS has been designed with the goal of being able to replicate our analyses across other samples and triangulate our findings with those arising through use of alternative genetically sensitive research designs. For this reason, we have built in overlap between CoTEDS and TEDS as well as other genetically informative cohort studies to ensure that we assess many of the same phenotypes at corresponding stages of development. To date, these cohorts primarily include the prospective adoption study, the Early Growth and Development Study (EGDS; Leve et al., 2013), and two transgenerational prospective observational studies, the Norwegian Mother and Child Birth Cohort Study (MoBa; Magnus et al., 2016) and the Avon Longitudinal Study of Parents and Children (ALSPAC; Boyd et al., 2013). Ongoing data collection from EGDS, MoBa and ALSPAC encapsulates longitudinal phenotypic and genomic information on parents and offspring from prenatal stages through childhood. As CoTEDS progresses, we will explore opportunities for further overlap with additional databases. By ensuring that we employ a combination of research methodologies in our work, we will be more likely to reach valid and robust research conclusions (Rutter et al., 2001).

Recruitment

Parents are recruited to CoTEDS from the sample of approximately 20,000 contactable adult twins who remain enrolled in the TEDS. The initial TEDS recruitment strategy, retention information and sample characteristics have been described in detail elsewhere (Haworth et al., 2013; Oliver & Plomin, 2007; Rimfeld et al., 2019; Trouton et al., 2002). Recruitment to CoTEDS commenced in March 2016 (data collection was launched the following year), with all TEDS twins invited to register their existing offspring online. CoTEDS registration for existing offspring and/or pregnancies is advertised to all TEDS families (both twins and their parents) during TEDS data collection, on the TEDS website, in the

Table 1. Child ages at CoTEDS registration and the total registered sample in May 2019[a]

Child age (years)	Number of children registered at this age	Number of children at time of writing at this age
0–1	260	82
1–2	99	126
2–3	76	113
3–4	46	89
4–5	28	50
5–6	25	42
6–7	11	25
7–8	6	19
8–9	2	6
9–10	0	1
10–11	1	1
Total	554	554

[a]Children registered between March 2016 and May 2019. New children registered on a continual basis.

annual TEDS newsletter, on social media, annual email circulars and by word of mouth when researchers have contact with TEDS families. Recruitment efforts are continually maintained.

CoTEDS registration includes a short screening procedure to confirm that the inclusion criteria are met for data collection: (1) the child must be a biological offspring of the TEDS twin and (2) the child must have regular contact with the TEDS twin (for twins not living with their offspring, we require that they have at least 1–3 h contact time per week; contact time is recorded for use as a covariate in analyses). We aim for twins to register their offspring at birth; however, there is no maximum child age for registration. Furthermore, we aim to register as many biological children per TEDS twin as possible, including twins in the offspring generation (as of May 2019, 2.4% of all registered births in CoTEDS are multiples [13 twin–pairs], as compared to national statistics showing that 1.6% of all British births in 2017 were twins; Ghosh, 2019). Child ages at registration are detailed in Table 1 for all registrations between March 2016 and May 2019. These children are registered to 435 twins (79.8% female), which includes 45 twin-pairs (where both twins in a pair have at least one registered child; 51% MZ) and 345 individual twins (of which 46% are from an MZ pair).

At each wave of data collection, twins provide informed consent and are given the option to share contact details for their child's co-parent (this may be the child's other biological parent and/or the twin's partner). Co-parents are recruited to take part in CoTEDS for the equivalent single wave of data collection. Co-parents are not recontacted for CoTEDS unless the twin nominates them again at a subsequent wave of data collection. The nature of the relationship between CoTEDS children and the co-parent providing data at each wave is carefully tracked.

Data Collection Protocol

Data collection is continually maintained alongside recruitment. The first wave of data collection (Wave 1) was launched in May 2017, involving a parent-reported questionnaire for the parents of 1-year-old CoTEDS children. The target child age for questionnaire completion is 12 months, but data are collected for all children between 12 and 23 months, with child age included as a covariate for analyses. The questionnaire is sent to participants to complete in their own time, taking approximately 60 min to complete online or on paper. Baseline information is collected for general demographic data and the composition and living situation of the immediate family. A battery of measures, described below, is then completed to assess several child, parenting, parent and socioecological phenotypes. Items relate to the perinatal period, first 12 months of the child's life and the weeks prior to questionnaire completion. Quality control items are used to monitor participant attention and validity of responses in sections that use large matrices of items measured along the same Likert scale. These quality control items require participants to select a specific response to the Likert scale. During data analysis, researchers will have the option to exclude participant responses on any given measure if quality control items are answered incorrectly. Prior to the launch of Wave 1, the full questionnaire battery was piloted in a sample of 195 community volunteers with infant children, who also provided quantitative and qualitative feedback on the questionnaire. Psychometric properties and participant feedback were assessed for all scales, and questionnaire edits made where appropriate.

Data collection commenced for the second wave of data collection (Wave 2) in October 2018, for the parents of 2-year-old children (target age 24 months). An adapted, age-appropriate version of the Wave 1 questionnaire is used at Wave 2, with the addition of three parent-assessed tests of child cognitive ability that are completed by parents after the questionnaire (see Table 2; Saudino et al., 1998). The Wave 2 battery was piloted in a sample of 210 community volunteers with infant children, who again provided quantitative and qualitative feedback. As with Wave 1, the Wave 2 pilot data were used to inform the composition of the final Wave 2 questionnaire. At the time of writing, we are developing the third wave of data collection (Wave 3) for the parents of 3-year-old children. As depicted in Figure 2, all parents complete data collection waves as applicable to their child's age at CoTEDS registration. Children who are registered before their first birthday follow the standard protocol, with parents invited to complete Waves 1–3 on, or shortly after, the child's corresponding birthday (see Figure 2, black arrows). Any parents registering a child older than 23 months will be invited to retrospectively complete a subset of baseline questions from Wave 1, after they have completed any other applicable waves of data collection (see Figure 2, grey arrows).

Measures, Waves 1 and 2

Within the space constraints of the Wave 1 and 2 questionnaires, we included key phenotypes that have previously been theoretically or empirically related to the development of cognitive and mental health-related traits in children. Where possible, we have used well-established, documented and validated measures. Where no sample-appropriate, questionnaire-based measure with adequate psychometric properties could be found, we designed our own. A summary of the measures, including number of items and overlap between CoTEDS Waves 1 and 2, is outlined in Table 2. For some phenotypes, the number of items differs between waves if edits were made to ensure that measures were age-appropriate and/or to accommodate space constraints in each questionnaire. Table 2 also details intentional measurement overlap with other genetically informative cohort studies.

Table 2. Summary of measures included in CoTEDS Waves 1 and 2

Phenotype	Measure	Number of items		Subscale(s)	Measure included in TEDS, EGDS, ALSPAC or MoBa[a]	Reference
		Wave 1	Wave 2			
Child						
Medical	Pregnancy	26	–	Duration, supplements, substance use, medical	TEDS	Created for TEDS and CoTEDS
	Birth	5	–	Duration, medical	TEDS	Created for TEDS and CoTEDS
	Health	11	7	Health at birth, hospital stays, specific health or development problems, antibiotic use	TEDS	Created for TEDS and CoTEDS
Temperament	Infant Toddler Social and Emotional Assessment (ITSEA)	12	12	Aggression/defiance	MoBa	Carter et al. (2003)
	Infant Characteristics Questionnaire (ICQ)	11	11	Fussy/difficult	EGDS, MoBa	Bates et al. (1979)
	The Emotionality, Activity and Shyness Temperament Survey (EAS)	25	25	Emotionality, activity, shyness, sociability, attention span-persistence	ALSPAC, MoBa	Mathiesen and Tambs (1999), Rowe and Plomin (1977)
	Perceived crying problem	1	1	–	–	Created for CoTEDS
Sleep	Brief Infant Sleep Questionnaire (BISQ)	11	11	–	–	Sadeh (2004), Sadeh et al. (2009)
	Perceived sleep problem	1	1	–	–	Created for CoTEDS
Soothing techniques	Use of comfort object/thumb sucking	3	3	–	–	Created for CoTEDS
Feeding (breastmilk)	Duration, exclusivity and difficulty	8	3	–	TEDS	Created for TEDS and CoTEDS
Feeding (solids)	Age started	–	1	–	–	Created for CoTEDS
	Perceived feeding problem	1	2	–	–	Created for CoTEDS
Developmental milestones	The Denver Developmental Screening Test	21	–	Personal-social, fine motor, gross motor, language	ALSPAC	Frankenburg and Dodds (1967)
Cognitive development	Parent Report of Children's Abilities (PARCA): parent report	–	26	–	TEDS	Created for TEDS; Saudino et al. (1998)
	Parent Report of Children's Abilities (PARCA): parent-assessed child tasks[b]	–	1, 7, 8	Paper folding, copying actions, matching shapes	TEDS	Created for TEDS; Saudino et al. (1998)
Language development	Languages and bilingualism	1	3	–	–	Created for CoTEDS
	Vocabulary, adapted from the MacArthur Communicative Development Inventory (MCDI)	–	30	–	TEDS	Created for TEDS, adapted for CoTEDS; Dale et al. (1998), Fenson et al. (1994)
	Sentence Complexity, adapted from the MacArthur Communicative Development Inventory (MCDI)	–	13	–	TEDS	Created for TEDS; Dale et al. (2000), Fenson et al. (1994)
Psychopathology	Strengths and Difficulties Questionnaire (SDQ) for 2–4-year-olds	–	25	Prosocial, hyperactivity, conduct problems, emotional problems, peer problems, total difficulties	TEDS, ALSPAC	Goodman (2001)
	Infant Toddler Social and Emotional Assessment (ITSEA)	–	13	Maladaptive behavior	MoBa	Carter et al. (2003)
Twin zygosity	Zygosity questionnaire for young twins	17	–	–	TEDS	Goldsmith (1991), Price et al. (2000)

(*Continued*)

Table 2. (*Continued*)

Phenotype	Measure	Number of items		Subscale(s)	Measure included in TEDS, EGDS, ALSPAC or MoBa[a]	Reference
		Wave 1	Wave 2			
Parenting						
Behavior	Parental Cognitions and Conduct Toward the Infant Scale (PACOTIS)	11	11	Parental hostile-reactive behaviors, parental overprotection	–	Boivin et al. (2005)
	Parent-Infant Caregiving Touch Scale	12	11	Holding, affective communication, stroking	–	Koukounari et al. (2015)
	The Parenting Scale	–	11	Verbosity, over-reactivity, laxness	EGDS	Arnold et al. (1993)
	Parental language input behavior	–	10	–	–	Created for CoTEDS
	Response to child at night	1	2	–	–	Created for CoTEDS
	Feeding child 'on demand'	1	–	–	–	Created for CoTEDS
Feelings	Parental Cognitions and Conduct Toward the Infant Scale (PACOTIS)	11	11	Parental self-efficacy, perceived parental impact	–	Boivin et al. (2005)
	Parental Feelings Questionnaire (PFQ)	7	7	Negative feelings toward the child, positive feelings toward the child	TEDS	Deater-Deckard (2000)
	Parenting Daily Hassles (PDH)	12	5	Frequency of hassles, intensity of hassles, parenting task hassles, challenging behavior hassles	EGDS	Crnic and Greenberg (1990)
Beliefs and principles	Baby Care Questionnaire (BBQ)	20	–	Structure, attunement	–	Winstanley and Gattis (2013)
Play	Parent Play Questionnaire (PPQ)	13, 17	16, 11	Frequency of parent–child play, parent attitudes toward parent–child play	–	Created for CoTEDS
	Parent and child comfort with risky play	–	18	Rough and tumble, lost/disappear/ unsupervised, speed, height, dangerous elements, tools	–	Created for CoTEDS
	Comprehensive parenting behavior questionnaire 2–3 years	–	6	Challenging behavior	–	Adapted for CoTEDS; Majdandžić et al. (2016)
Digital media use	Parent Play Questionnaire (PPQ)	3	12	Frequency of child watching digital media, frequency of child play with digital media, nature of child digital media use	–	Created for CoTEDS
Childcare	Maternity/paternity leave and childcare provision	7	2	–	TEDS	Created for TEDS and CoTEDS
Parent						
Depression	Edinburgh Postnatal Depression Scale (EPDS)	10	–	–	TEDS, EGDS, ALSPAC, MoBa	Cox et al. (1987)
	Major depression during child's pregnancy and first year after birth	6	–	–	MoBa	Kendler et al. (1993)
	Short Mood and Feelings Questionnaire (SMFQ)	–	13	–	TEDS (in offspring), ALSPAC (in offspring)	Angold et al. (1995)
Anxiety	Generalized Anxiety Disorder–7 (GAD-7)	–	7	–	–	Spitzer et al. (2006)
	Adult version of the Revised Child Anxiety and Depression Scale (RCADS)	–	20	Separation anxiety, generalized anxiety, obsessive-compulsive, social anxiety, panic	EGDS	Adapted for CoTEDS; Chorpita et al. (2000), Gregory et al. (2011)
Irritability	The Affective Reactivity Index (ARI)	–	7	–	–	Stringaris et al. (2012)

(*Continued*)

Table 2. (*Continued*)

Phenotype	Measure	Number of items		Subscale(s)	Measure included in TEDS, EGDS, ALSPAC or MoBa[a]	Reference
		Wave 1	Wave 2			
Substance use	Alcohol Use Disorders Identification Test (AUDIT)	–	10	Alcohol consumption, drinking behaviors, alcohol-related problems	TEDS (in offspring), ALSPAC (in offspring), MoBa	Saunders et al. (1993)
	Smoking	–	8	Cigarettes, electronic cigarettes	–	Created for CoTEDS
	Recreational drug use	–	5	Cannabis, sedatives, stimulants, hallucinogens, opioids	–	Created for CoTEDS
Sleep	The Pittsburgh Sleep Quality Index (PSQI)	18	18	Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, daytime drowsiness	TEDS, EGDS	Buysse et al. (1989)
	Sleep disruption due to child	9	9	–	–	Created for CoTEDS
	Night shifts	1	1	–	–	Created for CoTEDS
Therapy service use	Receipt of psychological treatment/therapy	2	2	–	EGDS	Created for EGDS
Psychiatric diagnoses	Lifetime diagnosis of a psychiatric disorder	1	–	–	–	Davis et al. (2018)
Romantic relationship	Behavior Affect Rating Scale (BARS)	22	22	Warmth, hostility	EGDS	Cui et al. (2005), Melby et al. (1995)
	Relationship quality	6	–	Happiness, satisfaction, commitment	EGDS	Conger et al. (2011)
Socioecological						
Home environment	Living situation	4	–	Type of home, household density	–	Created for CoTEDS
	Confusion, Hubbub, and Order Scale (CHAOS)	11	–	Calm, chaos	TEDS	Matheny et al. (1995)
Quality of life and social support	World Health Organization's Quality of Life Instrument-short version (WHOQOL-BREF)	–	11	Environment, social relationships	MoBa	Skevington et al. (2004)
	Involvement of other adults	3	3	Parenting support, financial support, other adults living in the home	–	Created for CoTEDS
	Family financial questionnaire	6	–	Material needs, making ends meet	EGDS	Conger et al. (1992)
	Financial strain	1	–	–	–	Created for CoTEDS
Socioeconomic status	Income sources and amount	6	–	–	TEDS	Created for TEDS and CoTEDS
	Parent highest educational qualification	1	–	–	TEDS	Created for TEDS and CoTEDS
	Parent occupation	3	1	Employment status, occupation classification	TEDS	Elias and Birch (2010)

[a]TEDS, Twins Early Development Study; EGDS, Early Growth and Development Study; ALSPAC, Avon Longitudinal Study of Parents and Children; MoBa, Norwegian Mother and Child Birth Cohort Study.
[b]Parent-assessed tasks of child cognitive ability — completed by parents with the child, after the questionnaire battery.

Future Directions

Data Collection

Following the development and launch of Wave 3, we plan to continue with further waves of data collection to be completed as the children of TEDS twins grow older, including questionnaire-based measurements of new age-appropriate phenotypes post infancy (e.g. comprehensive measures of child psychopathology and cognitive development, as well as parenting measures relating to early and middle childhood). Alongside questionnaire-based measures, we plan to collect other forms of data, for example, using observational methods to examine parent–child interactions (e.g. Ginsburg et al., 2006; Oliver & Pike, 2019). We will focus on developing our study design to enable longitudinal data collection from a range of sources within our ever-growing sample. New possibilities include harnessing in-home technologies to reach families, for example, using video calls or gamified mobile applications to remotely examine traits and parent–child relationships. Future directions include plans to collect genotype data from the children and partners of TEDS twins, to maximize learning

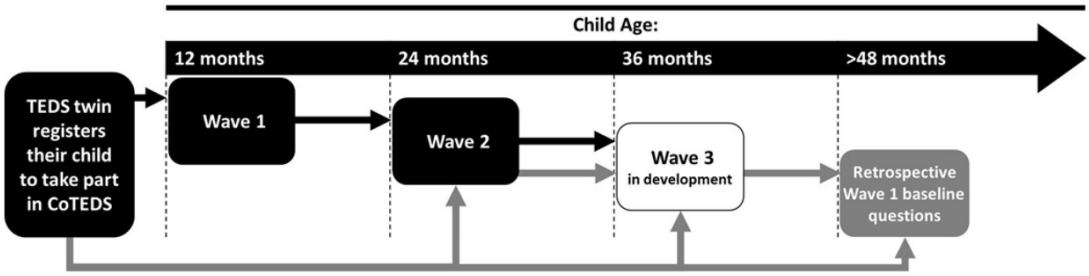

Fig. 2. Data collection protocol in May 2019.[a]
Note: [a]Black arrows: CoTEDS children registered before their first birthday follow the standard protocol from 12 months. Grey arrows: CoTEDS children registered after their second birthday complete any waves applicable to their age, followed by retrospective Wave 1 baseline questions.

from our two-generation pedigree analyses with state-of-the-art methods in statistical genetics.

Data Analyses

Opportunities to examine genetic and environmental intergenerational effects will be rich in CoTEDS, using longitudinal data relating to the phenotypes described in Table 2, alongside data from the main TEDS study. The number of twin-pairs with children required to reach 80% power to detect intergenerational genetic transmission of varying magnitudes has been estimated elsewhere by McAdams et al. (2018). Crucially, the authors show that the required number of twin-pairs is reduced if data on two or more children are included per twin (i.e. using the multiple-children-of-twins [MCoT] design). Furthermore, by examining twin phenotypes measured in TEDS and offspring phenotypes measured in CoTEDS, we can also include twin-pairs where only one twin in the pair has children in CoTEDS. Including these 'incomplete' extended families will allow us to maximize the number of avuncular associations in extended MCoT models. We therefore expect that our first genetically informed intergenerational analyses in CoTEDS will use data from all combinations of twin-pairs with children (i.e. one child per twin, two children per twin and incomplete extended families). Recruiting nonbiological offspring of TEDS twins to CoTEDS (e.g. children conceived via egg or sperm donors or adopted children) will be another possible avenue to increase power for extended MCoT analyses in the future. Further analyses will have the potential to span three generations across time, by combining longitudinal data on TEDS twins, their parents and their offspring. Hence, we will also be able to ask questions relating to societal and cultural changes across generations. Triangulating this work with analyses in other datasets will enable us to make a robust contribution to the literature regarding associations between parents and children during early child development.

Summary

CoTEDS will include genetically sensitive, prospective information on both parents and their offspring from infancy. As the number of children born to TEDS twins continues to increase over the coming years, CoTEDS is in place to develop an invaluable resource for the examination of genetic and environmental factors that shape child development, helping us to better understand the role that parents play in this process.

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Conflict of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethical approval was granted by the Psychiatry, Nursing and Midwifery Research Ethics Subcommittee, King's College London.

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7. Discussion

The aim of this thesis was to investigate the role of intergenerational parent-child effects and genetic transmission in familial risk for internalising. I approached this aim in the context of three challenges, discussed below.

7.1. Overview of findings in the context of thesis aims

7.1.1. Looking across time: temporal change and transactional associations between generations

Through the chapters of this thesis I aimed to contribute new knowledge on temporal change and transactional pathways in associations between parent and offspring internalising problems, within a genetically informed framework. Through a systematic review and meta-analysis in Chapter 2, I showed how little we know about these longitudinal processes in the context of parent anxiety in families. I showed evidence for significant associations between *concurrent* measures of parent anxiety symptoms and offspring internalising problems, which were not confounded by genetic relatedness. At the time of writing, only three studies had used longitudinal data to explore whether these associations reflect causal processes that endure across time (Ahmadzadeh et al., 2019; Brooker et al., 2015; Gjerde et al., 2018). One of the three papers referenced here was my own study, included in Chapter 3 of this thesis (Ahmadzadeh et al., 2019). In Chapter 3 I showed novel evidence for prospective prediction from child anxiety symptoms to mothers' anxiety symptoms during middle childhood, using a longitudinal adoption design. The adoption design allowed me to draw causal inferences as to the nature of the parent-offspring association, by ruling out the possibility of genetic confounding. I could not directly test for causal pathways using 'gold standard' experimental methods, because it is not possible (and, specifically, not ethical) to observe parents' reactions to experimentally induced anxiety in their children across a number of years. However, my results support causal evidence from experimental research where *treatment* of child anxiety is shown to be associated with a reduction in parent anxiety (Creswell et al., 2020; Lavallee, Schuck, Blatter-Meunier, & Schneider, 2019). My results add to existing experimental literature by suggesting that child-to-parent anxiety effects may exist naturally in an epidemiological context, where researchers have not intervened in the family environment. Therefore, I emphasise the importance of considering the possible impact of child symptoms on caregivers in the context of familial risk for internalising problems.

In Chapter 4 I used an Extended-Children-of-Twins (ECoT) design to explore direction of causation in a cross-sectional association between parental criticism and offspring internalising symptoms during adolescence. Only one study has previously been conducted using this method to examine adolescent internalising problems, in the context of maternal emotional overinvolvement (Narusyte et al., 2008). I detail corrections to their model specification in this

thesis. However, in this instance I was unable to discern evidence for a causal direction of effects between parental criticism and adolescent internalising symptoms. This is likely due to the aetiological structure of each trait being too similar, and therefore indistinguishable given the sample size and power in my analyses. It is also possible that causal effects existed concurrently between generations in both directions. Or, the intergenerational association, albeit non-genetic, could have been confounded by causal factors in the family environment (i.e., if unmeasured, environmental factors jointly influenced parent and offspring phenotypes). Further research is warranted to explore these possibilities. In Chapter 5, I combined developmental models with a Multiple Children-of-Twins/Siblings (MCoTS) design, to examine whether longitudinal change in mothers' internalising symptoms was associated with change in child temperament during early development. Of the four temperament characteristics studied, I found substantive evidence only for intergenerational correlations involving infant emotionality (not activity, shyness or sociability). Approximately half of the stable, baseline correlation between infant emotionality and mothers' internalising symptoms was explained by their genetic relatedness. Data showed no substantive evidence for longitudinal co-development of these phenotypes across time. Therefore, in this instance, change in mothers' internalising symptoms did not appear to be relevant to developmental change in offspring temperament characteristics across time. Chapter 5 provides a stepping-stone for new avenues of genetically informed research using longitudinal data, shining light on ways to combine developmental and genetically informed models.

In Chapter 6, I outlined the development of a new Children-of-Twins database: The Children of the Twins Early Development Study (CoTEDS). This database combines information on internalising symptoms among parents and their offspring from birth, alongside a broad battery of other measures. CoTEDS provides an unprecedented opportunity to examine how adult internalising problems change before and during parenthood; how offspring internalising problems develop in tandem with parent problems; and how offspring internalising behaviours compare to their parent's behaviour at the same age. I outline our efforts taken in CoTEDS to use measurement tools already employed in other genetically informed cohorts and to conduct repeated measurements across time, to facilitate longitudinal research that is replicable in other samples. In sum, the chapters of this thesis contribute new lessons and direction for future research examining how familial risk for internalising symptoms develops *across time*.

7.1.2. Improving generalisability of genetically informed research: looking beyond mother-child dyads in twin and adoption samples

The second overarching aim of this thesis was to broaden out analyses to include a range of different family members and move beyond use of highly niche samples where possible, to support the development of more generalisable results. In Chapter 2 I showed that most of the genetically informed, intergenerational research conducted to date in the context of parent anxiety and offspring internalising problems had been derived from parents who had undergone adoption or IVF, or who were twins. Most studies used only one parent (typically the mother) and one child

per family. The same was found in a previous review of all genetically informed intergenerational studies examining exposure to parental depression (most studies had been conducted using adoption designs with only one child and one parent per family; Natsuaki et al., 2014). The absence of fathers in research and the reliance upon data from adoptive parents or parents who are twins may create problems with the generalisability of results. In Chapter 3 I examined anxiety symptoms in adopted children, their adoptive mothers *and* fathers, and birth families. My results showed differences in parent-offspring anxiety associations between adoptive mothers and fathers, with evidence for father-to-child and child-to-mother effects. Results also highlighted the possibility of between-parent anxiety effects, whereby mothers' anxiety symptoms prospectively predicted fathers' symptoms. These findings would be masked, or possibly misconstrued, in research that did not simultaneously examine data from both parents. Related results have been shown in previous EGDS research where symptoms in one parent become more associated with child symptoms if symptoms are also present in the other parent (i.e., a statistical moderation effect; Hails et al., 2019). Together, our results emphasise the importance of taking a family-systems perspective where possible, including as many family members as there are data for and examining the interactions between them, to consider family-wide risk for internalising problems (Davies & Cicchetti, 2004). In subsequent chapters I sought to test hypotheses in different samples, to explore intergenerational risk for internalising problems among families who had not undergone adoption.

In Chapter 4 I combined data from two Swedish twin cohorts: a sample of adult twins with one child per twin (Neiderhiser & Lichtenstein, 2008) and a sample of adolescent twins with one parent per pair (Lichtenstein, Tuvblad, Larsson, & Carlstrom, 2007). As in several previously published ECoT studies (e.g., Hannigan, Rijsdijk, et al., 2018; Narusyte et al., 2008; Silberg, Maes, & Eaves, 2010), this approach produced a genetically informative dataset that did not exclusively comprise twins in either generation. This could help to dampen any biases associated with samples where all parents or all offspring are twins. Further, I proposed correction to model specification that had not been considered in previous research using the same samples. In Chapter 5 I explored alternative ways to model data from as many different extended family types as possible, by combining data from the Norwegian Mother, Father and Child Cohort Study (MoBa; Magnus et al., 2016) with Norwegian birth registry data. Building on methods used in previous research (e.g., Gjerde et al., 2019; Hannigan, Eilertsen, et al., 2018), I used ancestry information spanning four generations to identify >16,000 additional extended families linked by mothers who were cousins, or unrelated mothers who were sisters-in-law or cousins-in-law, who had not previously been included in MoBa MCoTS analyses. As in the ECoT design described in Chapter 4, the MCoTS design enabled me to incorporate data from siblings in the offspring generation, this time using children who were twins, full-siblings or half-siblings. It is not possible for parents to have an equal relationship with each of their children, given the transactional nature of parent-child relationships (Sameroff, 2009), and offspring of different ages will be differentially exposed to variation in their parents' behaviour across different stages of their development. Since most parents have more

than one child, it makes sense to model multiple parent-offspring relationships per family, where possible. Information on child siblings helped me to gain more precise estimates for: (1) phenotypic parent-offspring correlations (by including four parent-offspring correlations per extended family); (2) aetiology of offspring traits (i.e., by including siblings with different levels of genetic sharing and who share a home environment, to facilitate estimates of genetic [A2] and shared environmental influences [C2] on offspring traits); and (3) genetic covariance between parent and offspring traits (i.e., by including four avuncular correlations per extended family). In Chapter 6 I outlined ways in which Children-of-Twins data from CoTEDS can be modelled in future research to include any size family (i.e., twins with any number of children between them), and the possibility of combining CoTEDS analyses with data from other cohorts. In sum, within the chapters of this thesis I explored ways to simultaneously model information from multiple family members; pool data from cohorts that use the same measures; and identify novel data sources (e.g., in registry data) to index broader family structures that are less niche and therefore more representative of the general population. By indexing a wider pool of participants, it can be expected that results move towards more reliable and generalisable conclusions relating to familial risk for internalising problems.

7.1.3. Considering statistical power to identify genetic transmission effects on parent-offspring internalising associations

The third and final overarching aim of this thesis was to address uncertainties relating to the detection of genetic confounding in parent-offspring internalising associations. As outlined in the introduction (Chapter 1) of this thesis, most studies that have sought to distinguish genetic confounding from potential causal effects in associations between parent and child internalising have found no evidence for genetic effects. This is surprising, given the heritability of internalising problems across the lifespan (Hettema, Neale, & Kendler, 2001; Rice & Thapar, 2009; Sullivan, Neale, & Kendler, 2000). It is possible that the methods used in prior studies may have been insufficient to detect genetic transmission effects either because they were adoption studies using poor proxy measures; underpowered Children-of-Twins studies; or sibling comparison studies that do not provide an isolated estimate for genetic effects. In Chapter 3 of this thesis I explored use of proxy-measures for the detection of genetic transmission effects in an adoption design, using broad, composite scores for lifetime internalising problems, as well as total psychiatric problems, among birth parents and their first-degree relatives. Through these measures I aimed to capitalise on the shared genetic architecture of psychiatric symptoms among birth parents (Caspi et al., 2014; Waszczuk, Zavos, Gregory, & Eley, 2014), to derive a stronger proxy measure of child inherited risk for internalising. My results echoed the existing literature (e.g., Brooker et al., 2015; Eley et al., 2015; McAdams et al., 2015), yielding no evidence for genetic transmission effects in postnatal associations between parent and offspring internalising problems. As such, questions remain as to whether the proxy measure approach relied upon in adoption designs (i.e.,

comparing phenotypic information in birth parents and their offspring) has sufficient resolution to detect evidence for genetic transmission effects in the context of child internalising problems.

In Chapter 4 I moved on to explore statistical power in an ECoT design to detect significant effects of genetic confounding in associations between parental criticism and adolescent internalising symptoms. Here I outlined the factors that can limit statistical power in Children-of-Twins designs. I used simulated data to explore statistical power for the detection of genetic confounding in the context of my study variables and sample. Results varied depending on the strength of the intergenerational correlation that I assessed. I did not have 80% power to detect *low levels* of genetic confounding (i.e., accounting for <30% of the intergenerational association) in my main analyses. When I examined variables derived only from self-reported data, which showed lower intergenerational correlations, I did not have 80% power to detect *moderate levels* of genetic confounding (i.e., accounting for <50% of the intergenerational association). I emphasised the need for researchers to start incorporating power analyses in future Children-of-Twins studies, to facilitate critical interpretation of findings. In Chapter 5 I made use of a more powerful Children-of-Twins method, incorporating a wider range of extended family types (i.e., not just those linked by twin siblings) and up to two children per parent.

Previously published power calculations show that statistical power for the detection of genetic confounding is greatly improved in MCoTS models compared to traditional Children-of-Twins designs, through inclusion of multiple children per parent (McAdams et al., 2018). I added to the statistical power of this method by incorporating new extended family types, linked by parents who are cousins, sisters-in-law or cousins-in-law. Here, I showed novel evidence for genetic covariance linking stable baseline levels in mothers' internalising symptoms to stable baseline levels in offspring emotionality during the first five years of life. My genetic findings mirrored recent results in the same sample for symptoms of parent depression and child psychiatric symptoms (Gjerde et al., 2019). As such, I help to show that genetic confounding *is* observed in Children-of-Twins research for parent and child internalising phenotypes when statistical power is sufficient, at least during early childhood. As discussed in Chapter 6, we are seeking to include multiple children per twin in CoTEDS, to facilitate sufficiently powered analyses in this cohort as soon as possible. In sum, the chapters of this thesis highlight the importance of considering the limits of statistical methods for the detection of genetic confounding in intergenerational research. Moving forwards, it will be important to conduct studies using as many different research designs as possible. Triangulation of methods would help to overcome the biases associated with any single method and produce robust conclusions when results from multiple studies converge (Rutter, Pickles, Murray, & Eaves, 2001).

7.2. General Limitations

I have discussed the limitations associated with each particular study throughout the chapters of this thesis. In the following paragraphs I consider key limitations relevant to this research effort in

sum. These limitations reflect challenges that apply to all studies examining intergenerational risk for internalising problems, including my presented research.

7.2.1. Lack of diversity among research participants

All cohorts used for analyses in this thesis were derived from populations in Northern Europe or North America. Within these cohorts, parents were predominantly of European descent, with higher socio-economic status compared to their national average (with the exception of birth parents in the EGDS adoption cohort; Leve et al., 2019; Lichtenstein et al., 2007; Magnus et al., 2016; Neiderhiser & Lichtenstein, 2008; Kaili Rimfeld et al., 2019). Further, mental health data used across chapters of this thesis were positively skewed, indicating low levels of impairment among participants, and data were predominantly derived from mothers. Selection biases such as these (i.e., healthy, wealth and white) are an issue in most scientific studies involving voluntary research participation, influenced by factors at a global (e.g., inequality in research funding and infrastructure may lead to the clustering of cohorts in developed countries), national (e.g., cultural and societal factors may lead to gender and racial biases in research participation), institutional (e.g., lack of diversity among scientists who design and implement research protocol may lead to biases in research) and individual (e.g., higher levels of life stress can lead to lower capacity to engage in research) level.

As in all research, the findings in this thesis are specific to the context, or environment, in which they were derived. Caution must always be taken when extrapolating results to other contexts. For example, evidence shows that the heritability of complex traits, and genetic covariance between traits, can differ across societies and change within societies across time (K. Rimfeld et al., 2018; Wedow et al., 2018; Zavos et al., 2020). Non-shared environmental effects may be more influential in extreme situations (Plomin, 2011). Accordingly, gene-environment correlations can vary across families in different contexts. For example, whether or not parents respond with corporal punishment to genetically influenced aggressive behaviours in offspring is shown to vary in relation to family context, for example culture (Avinun, Davidov, Mankuta, & Knafo-Noam, 2018). The same could apply to parental criticism, as examined in Chapter 4 of this thesis. Cultural differences also exist in participant responses to mental health measures (Baxter, Scott, Vos, & Whiteford, 2013); with samples used to validate measures also subject to the same biases discussed above. For example, the Child Behaviour Checklist (CBCL) is one of the most widely used tools in mental health research (and this thesis) for examining child symptoms of mental distress (Achenbach, 1991). Despite having been translated into more than 80 languages and validated in dozens of societies (Ivanova et al., 2010; Ivanova et al., 2007), some research still suggests a lack of empirical support for measure use in low-income, diverse populations (LeBoeuf, Fantuzzo, & Lopez, 2010). Similar problems are reported for adult measures of internalising symptoms (Parkerson, Thibodeau, Brandt, Zvolensky, & Asmundson, 2015). Indeed, diversity in internalising symptoms across cultures, and lack of validated tools for their identification, can lead to under recognition or misidentification of psychological distress in

different groups (Kirmayer, 2001). Therefore, future research efforts aimed at understanding familial risk for internalising problems in a more diverse range of families must also involve consideration of the measurement tools used.

In sum, all research examining the heritability of human traits will lack generalisability to an extent, because all results are population specific. However, lack of diversity among participants used in this thesis and existing mental health research, and indeed lack of diversity among research communities, is a heavy limitation that reflects and perpetuates inequality in mental health risk (Cooper et al., 2013; Maura & Weisman de Mamani, 2017; Remes, Brayne, van der Linde, & Lafortune, 2016; Wilson, 2009; Yorke, Voisin, Berringer, & Alexander, 2016) and systemic racism in human and healthcare science (Nazroo, Bhui, & Rhodes, 2020; Rutherford, 2020; Saini, 2019; Salway et al., 2020). Moving forwards, it is the responsibility of researchers to continue emphasising these points. Further, we must actively seek ways to conduct robust research in new samples; develop culturally appropriate measures of mental health; new strategies for participant recruitment; and seek funding opportunities for research projects outside of Europe and to increase diversity among researchers. Without these efforts, we risk preserving a cycle of scientific evidence, and subsequent evidence-based policy, produced by and for groups who are, on average, privileged members of society. While the intergenerational correlations and genetic results presented in this thesis are valid and relevant for many families, they cannot be extrapolated to all.

7.2.2. Phenotyping in studies of internalising

7.2.2.1. Reporter biases

Practical and theoretical limitations relating to measurement validity in this thesis, and mental health research in general, require consideration. Across the chapters of this thesis, data concerning parent and offspring internalising symptoms were collected using questionnaire items. From a practical perspective, questionnaires are cheap and relatively simple to administer across the large samples required for genetically informed research. However, they rely exclusively upon participant perspectives and willingness to respond accurately. On the one hand, participant perspectives are what is important in research, especially in the context of understanding and conceptualising complex and subjective mental health phenotypes. On the other hand, participant perspectives are subject to a range of unwanted biases, such as participant social-desirability or recall bias. I was unable to examine reporter biases via comparison with other data sources, such as researcher rated interviews or observations (which in turn entail their own set of biases). When examining intergenerational associations, reporter biases are not a major issue if the rank order of each phenotype remains unaffected. That is, if biases result in everyone under- or over-reporting symptoms for any phenotypes of interest, we would not expect the correlation between those phenotypes to be seriously affected, as long as their rank order remained stable. However, problems arise if reporter biases differ between subgroups or result in a lack of variance in

participant responses. Although information from multiple sources can help to shed light on reporter biases in research, these data can give rise to additional challenges regarding whose perspective should be used and/or whether composite scores should be derived. For example, in Chapter 3 I showed that results differed depending on whether I used mothers' and/or fathers' reports of child anxiety, with the father-to-child anxiety effect only identified when including fathers' reports of child symptoms in the analyses. Similarly, in Chapter 4 I showed that the intergenerational association between parental criticism and adolescent internalising problems was almost halved when I excluded parents' reports of adolescent symptoms (i.e., using only adolescent self-reported symptoms). Ultimately, these disparities in my results, depending on whose reports I used, raised challenges in my ability to draw clear conclusions.

7.2.2.2. Measurement tools and protocol

The phenotypic data used in this thesis were also limited by the fact that questionnaires were kept purposefully short with infrequent repeat assessments, to maintain participant engagement and minimise burden. This means that we obtained only crude measures of participants' symptoms across time, which lacked detail as to the nature or context of their experiences. For example, only eight items were used in the MoBa cohort to measure mothers' symptoms of anxiety and depression, with a minimum of 12 months between assessments. More regular bursts of repeat data collection could improve research efforts in a number of ways. First, they could help to obtain more reliable, composite scores for participant mental health at any given time, which are less prone to error and bias compared to data collected at only one assessment. Second, they could shed light on different transactional associations or processes of co-development between parent and offspring symptoms, which may occur on shorter timescales compared to those examined in Chapters 3 and 5. Third, they could be used to inform on participants' proneness to fluctuations in symptoms across time, and to examine the impact of fluctuating mental health on intergenerational associations. My presented results are conducted within the practical limitations of the available data. As discussed in Chapter 6, we are now considering new methods to collect different forms of data remotely (i.e., not just questionnaire data) from parents in CoTEDS, using opportunities afforded by new technologies. This could include collecting video observations from families via smartphones or webcams (e.g., Oliver & Pike, 2019). We could also collect 'in-the-moment' data via active experience sampling and/or passive sensor data using devices in the home (Seifert, Hofer, & Allemand, 2018). These methods could help us to build a large-scale genetically informed cohort that also includes detailed phenotypic information from participants.

Alongside the practical limitations surrounding data collection, my attempts to define valid mental health phenotypes from data were limited from a theoretical perspective. All of the phenotypes examined in this thesis were complex human behaviours, defined based on years of existing psychiatric research. However, definitions in psychiatry are ever evolving as we seek better ways to categorise symptoms, whether that be in favour of new discrete conditions or transdiagnostic approaches (e.g., Caspi et al., 2014). In this thesis I took a transdiagnostic approach to defining

anxiety problems, as well as internalising problems more broadly, using measures that were not confined to disorder-specific criteria. For example, in Chapter 3 I used two broad definitions of child anxiety (i.e., one measure of general trait level anxiety and one measure combining clinically relevant anxiety disorder symptoms) to test the replicability of my findings. In Chapters 2, 4 and 5 I pooled items examining symptoms of anxiety and depression in children, adolescents and parents. As such, I aimed to capitalise on the shared genetic aetiology and phenotypic presentation across internalising problems (Kessler, Berglund, Demler, Jin, & Walters, 2005; Krueger & Markon, 2006; Waszczuk et al., 2014), while adding to the pre-existing literature that was focussed predominantly on parent depression (see Chapter 1 for an overview). Transdiagnostic approaches make sense from a research perspective, for understanding familial risk for highly comorbid phenotypes. However, results may not generalise to individuals who display only a specific cluster of symptoms (i.e., symptoms that adhere to only a single diagnostic criteria).

7.2.2.3. Accounting for comorbidity

Confining analyses to narrow symptom clusters is not straight forward, as it becomes necessary to account for the possible influence of other co-morbid problems. For example, of the studies reviewed in Chapter 2, one included controls for co-morbid symptoms of depression to refine their measure of parental anxiety (Gjerde et al., 2018). Thus, authors supposed that depression symptoms could act as a confounding cause for parents' anxiety and offspring internalising outcomes. However, it could also be possible for parent's anxiety to act as a cause for co-morbid depression symptoms. If true, then regressing out the effects of co-morbid depression symptoms was an 'overcorrection' in their analyses. Collinearity could also cause problems, as controlling for variance in depression could statistically diminish variance in anxiety, if the two were highly correlated. Difficulty in distinguishing narrow phenotypes in research is not confined within the boundaries of internalising problems, but applies to all forms of psychiatric distress (Caspi et al., 2014). Individuals who experience an internalising disorder are also at increased risk for experiencing externalising and/or psychotic problems at some point in their lifespan (Caspi et al., 2020; Kessler et al., 2005). As such, familial risk for internalising symptoms is not exclusive of risk for other forms of psychopathology. I did not control for measures of other psychiatric problems, to avoid over-correction of my results. However, it is important to acknowledge that results may differ if I had sought ways to account for psychiatric comorbidity, most likely by reducing the parent-offspring correlations that I observed.

Comorbidity and cross-trait associations are well-evidenced for internalising and externalising problems in particular (Angold, Costello, & Erkanli, 1999; Caspi et al., 2014; Kessler et al., 2005; McElroy, Shevlin, Murphy, & McBride, 2018). Comorbid externalising problems can involve alcohol and substance abuse, attention, hyperactivity or conduct problems in parents and/or offspring. As discussed in Chapter 1, parent internalising problems also reflect risk for offspring externalising problems (Barker, Jaffee, Uher, & Maughan, 2011; Beck, 1999; Collishaw et al.,

2016; Goodman et al., 2011; Kane & Garber, 2004; A. R. Kim & Sin, 2020; Silberg et al., 2010; Singh et al., 2011). It may be important to test *transactions between psychopathologies* during childhood, to avoid drawing spurious conclusions about one form of psychopathology, that are in reality confounded by another (Roos et al., 2016). For example, it is possible for the consequences of genetically influenced externalising symptoms to cause internalising symptoms during childhood, thereby acting as a causal mechanism in familial risk for internalising problems. Furthermore, children with co-occurring problems may represent a group with more severe symptomatology, who would not be identified in research focussing on just one class of symptoms (Oland & Shaw, 2005). This is also important to consider for parents, given that parental mental illnesses across *all* diagnostic categories have been associated with *all* child externalising and internalising domains of vulnerability (Dean et al., 2018). In sum, new research is needed to consider the interplay between all forms of mental distress in familial risk for internalising. New opportunities for in-depth phenotyping will be present in the CoTEDS sample, as we map developmental trajectories from birth in two generations. As detailed in Chapter 6, Table 2, we have sought to include a wide battery of measures in the CoTEDS assessments, including novel questionnaires developed for remote examination of the family environment and parent-child relationships (e.g., a novel measure of parent-child play: Ahmadzadeh, Lester, Oliver, & McAdams, 2020). We next plan to link study data with participant medical records. Further, we can now link questionnaire data in the MoBa with information from a range of national registries, including medical, education, criminal and social-welfare records. These linkages provide further opportunities to derive novel phenotypes relevant to the presentation of psychiatric distress in families.

7.2.3. Looking beyond the effects of gene-environment correlation (*r*GE) in parent-offspring correlations

Measured phenotypes are the result of an intricate web of genetic and environmental influences. In this thesis I have focussed on methods to control for confounding by passive *r*GE in associations between parent and offspring traits, to test whether it may be reasonable to draw causal inferences regarding the effect of parents and offspring on one another. I base my analyses and interpretation of results on knowledge regarding the genetic correlation between parent and offspring genomes, and robust evidence for biological pleiotropy of genes linked to complex human traits. That is, I know that offspring inherit 50% of their parent's genes, which can exert influence on a range of complex traits in both generations across time. As such, correlations between traits in parents and offspring can be confounded by influence of their shared genes. However, evidence for genetic covariance between parent and offspring traits could be, at least in part, attributable to processes that I do not explore in the chapters of this thesis. These are outlined below.

7.2.3.1. Mediated pleiotropy

Mediated pleiotropy (also referred to as vertical pleiotropy) refers to the process by which a genetic effect on one phenotype is mediated by an effect on another phenotype (Avinun, 2019). That is, genes influencing a parent phenotype can become correlated with a child phenotype, if the parent phenotype has a direct, causal influence on the child phenotype. In this instance, the genetic covariance between parent and child phenotypes is not attributable to a confounding effect of common shared genes, but rather comes about as a result of a genetically influenced parent trait *causing* a child trait (akin to an evocative gene-environment correlation whereby the parent's genes evoke changes in the child). However, in Children-of-Twins research we assume that parents' genes only become correlated with a child phenotype via their direct transmission to the child, where they exert causal influence on the child phenotype. This means that the effects of mediated pleiotropy will be incorrectly identified as sources of genetic confounding in Children-of-Twins research, leading researchers to 'over-correct' parent-child associations (McAdams, Rijsdijk, Zavos, & Pingault, 2020). In practise it is difficult to distinguish these genetic pathways. I use Children-of-Twins methods in Chapters 4 and 5. I find significant residual associations between parent and child phenotypes even after I control for the estimated influence of genetic confounding. This means that were I to have controlled for mediated pleiotropy as if it was a confounder, the effects were not so large that they made the residual parent-offspring correlation undetectable. Statistical caveats in identifying the true nature of genetic confounding can be bypassed in adoption designs, where parents and offspring are not genetically related. As such, it is important that we continue to use method triangulation to test hypotheses and check consistency of findings across research designs.

7.2.3.2. Gene-by-environment (GxE) interaction

GxE interactions reflect the process by which genetic effects on any given trait vary in relation to an individual's context or environment, and vice versa (Manuck & McCaffery, 2014). For example, children with high genetic risk for internalising problems may not develop symptoms if they experience a supportive environment, or their symptoms could be exacerbated if they experience a non-supportive environment (Belsky, Bakermans-Kranenburg, & van Ijzendoorn, 2007). In single-generation twin (and/or sibling) studies, heritability estimates (A) can be inflated if genes interact with environments that twins share (C). This is because MZ twins share more genes than DZ twins, so MZ twins will appear *even more similar* compared DZ twins if their shared genes interact with environments that also make them more similar. Heritability estimates (A) are deflated if genes interact with environments that twins do not share (E). This is because twins will appear *more different* if their shared genes interact with environments that make them less similar. Again, this process will be more pronounced for MZ compared to DZ twins, given that MZ twins share more genes. In two-generation Children-of-Twins studies, these processes can affect estimates of genetic covariance between parent and child traits, by altering estimates of parent and/or child heritability. Genetically informed adoption research can help to shed light on

instances where GxE interactions may operate. For example, findings from the EGDS cohort show evidence for GxE interactions in associations between infant emotionality and overreactive parenting (Lipscomb et al., 2012), as well as toddler behaviour problems and structured parenting (Leve et al., 2009). However, these studies rely upon the adoption method for approximating offspring genetic risk using birth parents' phenotype data. New MCoTS-GxE models have recently been used to examine individual differences in environmental sensitivity within a Children-of-Twins framework. Results suggest that some children in the MoBa sample appear more genetically susceptible than others to the negative effects of foetal exposure to maternal distress (McAdams et al., in prep). In future work I hope to start to unpack these processes further. For example, I will be able to explore whether children vary in their susceptibility to parent mental health postnatally (i.e., whether the genetic [A] and environmental [C/E] aetiology of child traits is moderated by the severity of parent mental health); or whether parent-child associations are moderated by environmental contexts (i.e., whether genetic [A1'] and phenotypic [*p*] transmission pathways are moderated by measures of the family environment).

7.2.3.3. Non-additive effects

Gene-gene interactions (i.e., epistasis, whereby the effect of one gene on a trait is altered or masked by the effect of another gene) and dominance effects (i.e., where the effect of one allele for a gene on a trait is masked by the effect of the other allele for the gene on the trait) are examples of non-additive effects that result in a non-linear association between an individuals' genetic 'risk' for a trait and their phenotypic presentation (Cordell, 2002). Similar to GxE interactions, these processes can bias heritability estimates and subsequent estimates of genetic covariance between generations. Dominance effects (D) can be estimated in Children-of-Twin research in place of latent variables for estimating effects of the shared environment (C) on a trait. However, this is problematic when both D and C are operating simultaneously. In support of the research published in this thesis, methodological work in quantitative genetics suggests that linear models are sufficient for the detection of variance explained by genetic influence in complex traits, since most variance appears additive, even if some genetic variants do act in complex, interactive, nonlinear ways (Hill, Goddard, & Visscher, 2008).

7.2.3.4. Epigenetics

It is possible for an individuals' environment to *physically affect* gene expression through epigenetic processes (i.e., biological changes that can affect gene expression without changes to the DNA sequence), such as methylation (Meaney & Szyf, 2005). In other words, gene *expression* can change as a function of the individuals' environment. DNA methylation is thought to be especially influenced by the prenatal environment, in line with the foetal programming hypothesis (Mill & Petronis, 2007). Epigenetic mechanisms can alter heritability estimates in twin and sibling research in a similar fashion to GxE interactions. That is, heritability estimates (A) are inflated if the environments exerting epigenetic changes are shared between twins/siblings (C),

or deflated if the environments are not shared between siblings (E). It *could* be possible for further problems to arise if epigenetic changes in one generation are then transmitted to future generations via changes to gene expression in gamete cells (as has been suggested in rodent studies; Heard & Martienssen, 2014; Meaney & Szyf, 2005). This is still unproven in humans and remains a controversial hypothesis, especially given that epigenetic signatures appear completely removed during gamete formation (Horsthemke, 2018). The degree to which transgenerational epigenetic inheritance would account for variance in offspring traits, and covariance with parent traits, remains unknown.

7.2.3.5. Associations between siblings and between parents

Throughout the chapters of this thesis I have focussed on modelling vertical effects in familial clustering of internalising problems (i.e., from parents to offspring). However, it is important to also note the possible influence of horizontal effects. These can operate between siblings, or between parent-offspring dyads in the same family, or between parents. Indeed, all parent-child relationships are part of a wider family context and most children grow up with siblings and two parents (Davies & Cicchetti, 2004). Sibling relationships are enduring and associated with children's social and emotional development (Drake & Ginsburg, 2012; Dunn, Slomkowski, & Beardsall, 1994). Evidence suggests that reports of sibling relationship quality are associated with child internalising problems (Fox, Barrett, & Shortt, 2002; J. Y. Kim, McHale, Crouter, & Osgood, 2007; Stocker, Burwell, & Briggs, 2002). Further, jealousy or perceived inequality in siblings' relationships with parents may be associated with familial risk for internalising (Lindhout et al., 2003; Oliver & Pike, 2018; Pike, Atzaba-Poria, & Kretschmer, 2016). While many genetically informed research designs rely on comparisons of sibling pairs to estimate the aetiology of complex traits, we know little about how sibling relationships, and their differential relationships with parents, might influence results (Oliver & Pike, 2018). Akin to parent-offspring associations, sibling associations can also be confounded by genetic relatedness and reflect influence by gene-environment correlation. While I have been able to include multiple children per parent in structural equation models presented in this thesis, I have not yet attempted to add further complexity by examining paths for sibling interactions. The same is true for interactions between parents.

Considerable resemblance between parents is found at a higher rate than would be expected by chance for many complex behaviours, including psychiatric traits (Nordsletten et al., 2016). This reflects the process of assortative (i.e., non-random) mating, whereby individuals have a tendency to select partners similar to themselves (Schwartz, 2013). In the context of familial risk for internalising problems, assortative mating between parents at a phenotypic level works to increase additive genetic variance among offspring. This is because both parents are more likely to pass on 'risk associated' alleles to their shared offspring (Peyrot, Robinson, Penninx, & Wray, 2016; Plomin, Krapohl, & O'Reilly, 2016). In the context of research presented in this thesis, assortative mating could have inflated genetic similarity between non-identical siblings, given that

they would be more likely to inherit the same 'risk associated' alleles from each parent. This is the case only for non-identical siblings, given that identical siblings (MZ twins) already share 100% of their genes. When assortative mating makes non-identical siblings more similar for a trait of interest within one generation, we would gain artificially inflated estimates for influence of the shared family environment (C) on that trait. Corresponding decreases in heritability estimates (A) would in turn influence intergenerational estimates of genetic covariance in Children-of-Twins research. Assortative mating could also increase non-genetic, causal processes underpinning familial risk for internalising, as offspring are exposed to psychiatric symptoms in *two* parents. The effects of assortative mating remain underexplored in the context of familial risk for internalising problems. However, endeavours to model two parents per child in Children-of-Twins research (Keller et al., 2009; Silberg & Eaves, 2004; Torvik et al., 2020) may now yield new knowledge, as suggested in section 7.3.1. of this chapter ('Avenues for Future Research').

Together, the limitations that I have outlined are intended to encourage readers to exercise caution against taking the findings of this thesis as definitive. Instead, they are part of a wider, evolving research effort. My presented findings are specific to the samples in which they were collected, the measures that were used and the phenotype definitions decided upon. Structural equation modelling provides a flexible framework for statistically representing complex theories, but, as in all research, the analyses reflect a simplified version of reality, confined within the statistical limits of the data. The aims of this thesis, focussed on understanding genetic confounding in parent-offspring internalising associations, can be developed in future research to incorporate other forms of gene-environment interaction and associations with other family members. In the meantime, we should not succumb to the illusion that the influence of genes and environments in familial risk for internalising problems can be easily separated. Family relationships are complex. The principles of gene-environment correlation can explain part of the picture, but they do not account for all mechanisms across all populations.

7.3. Avenues for Future Research

Opportunities for new research to expand our understanding of familial risk for anxiety and depression are vast. In the following sections I outline three possible routes to build upon the key aims, results and limitations of the studies presented in this thesis.

7.3.1. Explore ways to model broader family systems

A next step could be to expand my analyses to model broader family systems. This could involve examining parent-offspring associations in models that also account for associations between two parents and between siblings. For example, in Chapter 3 I presented triadic (mother, father, child) cross-lag panel models. Results showed a significant child-to-mother effect that existed over and above any effects involving the father or mother-to-child processes, which were simultaneously accounted for in the model. I could now seek to include associations between siblings in this framework, to explore whether results hold when sibling relationships, and parent-offspring

relationships for more than one child, are accounted for. I could use a similar structural equation modelling approach as presented in Chapter 5, incorporating latent factors to model group level information, leaving autoregressive and cross-lagged paths to capture individual-level data (Hamaker, Kuiper, & Grasman, 2015). This kind of research will be possible in the EGDS cohort, where data are currently being collected from genetically unrelated siblings reared together, as well as genetically related siblings reared apart (Leve et al., 2019). Although the principals of gene-environment correlation are typically applied to the study of parent-offspring relationships (Horwitz & Neiderhiser, 2011; Plomin, DeFries, & Knopik, 2012), it will be of interest to explore how they extend to a family systems perspective that incorporates sibling effects.

Child siblings are already included in MCoTS models. However, we do not explore child sibling effects and so lose nuance in information about their relationships, which may be important for the development of parent and child internalising symptoms. I now plan to consider ways to account for broader family systems within the MCoTS design. For example, I could explore ways to include information about the number of siblings in a family, or the difference in mental health phenotypes between siblings in a family, as moderators in MCoTS analyses. It may also be possible to expand MCoTS structural equation models to include causal, phenotypic paths between siblings, alongside paths for decomposing parent-offspring covariance. Again, this would help to inform on the nature of parent-offspring correlations, whilst accounting for influence of other relationships in the family.

Work to extend MCoTS models to include two parents per child in the MoBa has already commenced, in efforts to model the effects of assortative mating on parent-offspring correlations (Torvik et al., 2020). Specifically, authors sought to estimate similarity between partners in genetic factors for educational attainment, by comparing phenotypic correlations between adult parents and their siblings, adult parents and their partners, and adult parents and their sibling's partners (i.e., their in-laws). Partner resemblance in genetic factors for educational attainment was high (r=.73). Authors used this estimate of partner genetic resemblance to adjust offspring sibling correlations, to account for the inflation of siblings' genetic relatedness by non-random mating among parents (see section 7.2.3.5. of this chapter). Further, authors were able to model causal, phenotypic pathways for both mother-child and father-child associations, to explore differences in results between parents. This approach could be taken in future research on familial risk for internalising problems, and perhaps extended to include a causal pathway to model interactions between parents. Power analyses will be crucial to explore the sample sizes required to examine additional parameters in MCoTS models, to account for the influence of additional family members and gene-environment correlations.

7.3.2. Identify environmental influences in familial risk for internalising

Throughout this thesis I present evidence for non-genetic pathways linking internalising phenotypes in parents and offspring. Non-genetic pathways capture causal influence of the parent

and offspring phenotypes on one another. However, the possibility of environmental confounding is not ruled out (i.e., if aspects of the family environment act as a common cause for both parent and offspring phenotypes). As discussed above, environmentally mediated influence from co-parents and siblings could be included in future analyses. Further, factors outside of the family system are likely to have influence. For example, it is suggested that intergenerational associations involving maternal mental health may in part be due to broader environmental factors associated with the parents' risk for internalising problems, such as low socio-economic status, inadequate living conditions, poor social support or early parenthood (Barker, Copeland, Maughan, Jaffee, & Uher, 2012). Parent-child associations have also been found to be stronger among disadvantaged families (Lovejoy, Graczyk, O'Hare, & Neuman, 2000). Neighbourhood factors are found to be among the stongest correlates with parenting behaviours, alongside child temperament, the marital relationship and parent mental health (Belsky & Jaffee, 2006). Furthermore, reciept of support or treatment for psychiatric problems among parents and/or offspring who experience internalsing problems can exert influence on parent-offspring internalsing associations (e.g., Creswell et al., 2020; Lavallee et al., 2019). New research within a genetically informed framework is needed to explore the complex interplay between these factors, building on the work presented in this thesis.

In Children-of-Twins research, it is possible to model an intergenerational pathway to capture influence of environments that are shared by *all* individuals in an extended family (labelled C1'; McAdams et al., 2018). C1' could, for example, demonstrate the influence of social or cultural factors on parent-offspring correlations. C1' can be specified differently across familiy types, to account for the different degrees to which their environments are likley to overlap. However, many Children-of-Twins studies to date have not allowed for the possibility of an effect of the extended family environment. It only makes sense to model C1' in analyses where influence of the shared environment is present for the parent and/or offspring trait (i.e., in Chapter 4 I find no influence of C1 nor C2 in my analyses, so do not model C1'). Inclusion of C1' is shown to reduce statistical power for the detection of A1', although failing to account for C1' when it is infact significant can result in overestimation of A1' (McAdams et al., 2018). In Chapter 5 of this thesis I show that C1' was not significant in my analyses, so I was able to drop it from the models to maximise power to detect A1'. All MCoTS analyses inlcuding C1' thus far have been conducted in the Norwegian MoBa sample and have shown minimal influence of this parameter on parent-offspring covariance. In future research it would be useful to examine the influence of C1' in samples derived from less homogenous populations.

7.3.3. Making use of genomic data

In the chapters of this thesis I use family data to infer the role of genetic factors. However, as covered in the discussion of Chapter 2, new methods in genome-wide analysis are beginning to yield new opportunities for research, using measured genetic factors among family members. Genomic methods cannot yet replace the methods used in this thesis, given that they currently

only account for the additive effects of genetic variants tagged on DNA arrays, rather than approximating influence of the entire genome as in twin and family-based methods (Cheesman et al., 2017). However, there are ways that we can start to apply the methods currently afforded by genomic research to test similar hypotheses to those examined in this thesis. An especially attractive prospect of these methods is that they can be used with any samples comprising parents and children, rather than requiring targeted recruitment of adoptive or extended families. Further, they shed light on new mechanisms and perspectives in genetically informed family research. One example of this has been the concept of 'indirect genetic effects' (Eaves, Pourcain, Smith, York, & Evans, 2014), or 'genetic nurture' (Kong et al., 2018). Genetic nurture exists if genes in the parent generation become correlated with a child phenotype, over and above the effects of genes transmitted to the child. In other words, genetic nurture represents an environmentally mediated genetic effect of parents on their offspring, that is agnostic to any particular parent phenotype and is uncorrelated with child-specific genetic effects. While the methods used in this thesis are useful for pinpointing how specific parent traits are associated with the development of internalising problems in offspring, genomic methods can shed light on the broader influence of the parent genome on offspring internalising. For example, genomic methods can include use of polygenic scores or SNP-based variance decomposition approaches (as implemented in the Genome-wide Complex Trait Analysis [GCTA] toolkit; Yang, Lee, Goddard, & Visscher, 2011).

Polygenic scores are computed from DNA samples to measure individual-level genome-wide 'risk' for the development of different complex traits (Wray et al., 2014). Polygenic scores index the total number of all known trait-associated genetic variants inherited by an individual, weighted by the strength of each variant's association with the trait. When computed for both parents and offspring, polygenic scores can be used to explore the role of uncorrelated transmitted versus non-transmitted variants in phenotypic associations across generations. (Bates et al., 2018; Kong et al., 2018; Wertz et al., 2019). This approach is useful for identifying parental influence on any family-based phenotype of interest, by examining the influence of genes that are specific to parents (i.e., not transmitted to the child). For example, researchers have used polygenic scores associated with educational attainment to differentiate parent and offspring genetic influence on measures of parenting, shedding light on passive and evocative gene-environment correlations (Wertz et al., 2019). Further, they showed evidence for genetic confounding in associations between parenting and child educational attainment, as associations were reduced following correction for genetic influences (as measured by polygenic scores). Finally, mothers' genetic scores were associated with child educational attainment over and above children's own genetic scores, highlighting an effect of genetic nurture. Results such as these can complement findings from adoption and Children-of-Twins research, to inform on the different ways in which parents might influence offspring development. Research using polygenic scores to understand familial risk for internalising problems will become increasingly possible as we gain new knowledge about trait-associated genetic variants for a wider range of phenotypes, derived from larger samples.

Genomic variance decomposition methods involve calculation of genome-wide genetic relatedness matrices (Yang et al., 2011). The standard approach, Genomic-RElatedness-based restricted Maximum-Likelihood (GREML), harnesses the random genetic similarity that exists between unrelated individuals. If individuals who show higher levels of similarity in common genetic variants (single nucleotide polymorphisms, SNPs) also show higher levels of trait similarity, then genetic influence on that trait is inferred. Specifically, GREML derives SNP heritability estimates for traits, and decomposes genetic covariance between traits, using genomic covariation between individuals as opposed to that inferred from family structure. Intergenerational extensions of GREML (e.g., Trio-GCTA or Relatedness Disequilibrium Regression) can now be used to partition direct and indirect influence of parent and offspring genomes on child phenotypes (further, Trio-GCTA can partition the influence of mother, father and offspring genomes on phenotypes obtained from any family member; Cheesman et al., 2020; Eaves et al., 2014; Eilertsen et al., 2020). As with methods using polygenic scores, results are useful for determining the direction of effects between generations, as child influence is differentiated from parent influence. Further, GREML-based methods indicate *total* influence of parent traits on a child trait (as indexed by the parents' genome), up to the point at which the child trait was measured. This provides one way to bypass difficulties with phenotyping in large population samples (Cheesman et al., 2020). Recent findings suggest influence of genetic nurture on the development of child depression symptoms, which may load as influence from the shared family environment (C) in twin/sibling research (Cheesman et al., 2020). As such, new research in statistical genetics can complement the research efforts presented in this thesis, helping us to critically interpret results.

7.4. Final Conclusion

Symptoms of anxiety and depression have a high prevalence and high burden in our society. Vast numbers of children are exposed to these symptoms in their parents and are found to be at higher risk for developing similar symptoms themselves. However, there are significant gaps in our understanding as to how familial risk for anxiety and depression arises. Genetically informed research designs can help us to understand whether it is ever reasonable to draw causal inferences as to the influence of parent symptoms on the development of child symptoms. In this thesis I highlight the importance of also considering the influence of child symptoms on parents. I investigate ways in which parent and child symptoms might co-develop and present new methods to model these processes within a genetically informed framework. I maximise on use of existing datasets to conduct genetically informed research with many different types of parent-offspring pairs, moving away from a traditional focus on mother-child dyads in twin and adoption samples. In this way I hope to derive results that are more generalisable to wider populations. Further, I examine the strengths and limitations of existing genetically informed research designs, considering the limits of statistical power to detect the effects of genetic relatedness between parents and offspring. This work sits within a fast-evolving area of science, where new research

involving international collaborations and data from large-scale population cohorts is essential for deepening our understanding of the complex interplay of genes and environments in families. New research can now build on the findings presented in this thesis, which help to shed light on how internalising symptoms in parents and offspring can exert influence on one another across development, alongside the effects of genes shared within families.

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Appendix A

Supplementary materials for Chapter 2

Full search strategy

"mother* anx*" OR "matern* anx*" OR "father* anx*" OR "patern* anx*" OR "parent* anx*" OR "*natal anx*"

OR "mother* phobi*" OR "matern* phobi*" OR "father* phobi*" OR "patern* phobi*" OR "parent* phobi*" OR "*natal phobi*"

OR "mother* social* anx*" OR "matern* social* anx*" OR "father* social* anx*" OR "patern* social* anx*" OR "parent* social* anx*" OR "*natal social* anx*"

OR "mother* general* anx*" OR "matern* general* anx*" OR "father* general* anx*" OR "patern* general* anx*" OR "parent* general* anx*" OR "*natal general* anx*"

OR "mother* neurotic*" OR "matern* neurotic*" OR "father* neurotic*" OR "patern* neurotic*" OR "parent* neurotic*" OR "*natal neurotic*"

OR "mother* obsessive*" OR "matern* obsessive*" OR "father* obsessive*" OR "patern* obsessive*" OR "parent* obsessive*" OR "*natal obsessive*"

OR "mother* panic" OR "matern* panic" OR "father* panic" OR "patern* panic" OR "parent* panic" OR "*natal panic"

OR "mother* agoraphobi*" OR "matern* agoraphobi*" OR "father* agoraphobi*" OR "patern* agoraphobi*" OR "parent* agoraphobi*" OR "*natal agoraphobi*"

AND

child* OR adolescen* OR teen* OR youth* OR young OR offspring OR infan*

AND

twin OR twins OR sibling* OR adoption OR adopted OR "in vitro fertilization" OR "assisted conception" OR "cross-fostering" OR "instrumental variable" OR "quasi-experiment*" OR causa*

Discussion of seven excluded publications that accounted somewhat for bias by genetic confounding, but were not classified as using robust, genetically sensitive quasi-experiments

Of the 441 records screened, only eight publications met our inclusion criteria. Of the excluded publications, seven included design features that accounted somewhat for bias by genetic confounding. These studies and our reasons for their exclusion are outlined below:

Two studies of exposure to prenatal maternal anxiety used paternal anxiety symptoms as a 'negative control' for environmentally mediated prenatal transmission (Capron et al., 2015; O'Donnell, Glover, Barker, & O'Connor, 2014). The logic behind this design is that children can be exposed to *maternal* prenatal anxiety but are not directly exposed to *paternal* prenatal anxiety. Thus, equivalent prediction of child internalising by maternal and paternal prenatal mood would support a role for genetic transmission and provide evidence against an effect of foetal exposure to maternal anxiety. In the first of these studies, measures of paternal pre- and postnatal mood were included as covariates in analyses of mother-child associations, showing that mothers' prenatal anxiety persistently predicted offspring outcomes across childhood (O'Donnell et al., 2014). In the second publication, authors directly compared mother-child and father-child associations, demonstrating that only maternal prenatal anxiety symptoms predicted internalising problems in adolescent offspring (Capron et al., 2015). While these studies do go a long way towards controlling for potential genetic confounding between prenatal maternal anxiety and child internalising, the authors were unable to control for differences in offspring exposure to maternal and paternal anxiety symptoms *postnatally*. If offspring spent more time with mothers compared to fathers postnatally (which is likely in the societies they focus on), results could be skewed towards stronger mother-child associations. As such, we decided that these designs did not match our inclusion criteria. Next were studies that examined child exposure to parent state-level (i.e., current, transitory) anxiety symptoms, while controlling for parent trait-level (i.e., stable, longer-term) symptoms (Aktar, Majdandzic, de Vente, & Bogels, 2013; Henrichs et al., 2009; O'Connor, Heron, Golding, Beveridge, & Glover, 2002; O'Connor, Heron, Golding, & Glover, 2003; O'Donnell et al., 2014; Van den Bergh & Marcoen, 2004). Although not presented as such in these publications, measures of parent trait-level symptoms could be considered a proxy for overall genetic risk. However, any residual association involving the state-level symptoms could still be attributable to genetic mechanisms, so we decided to exclude publications using this design.

Re-running the meta-analyses for postnatal exposure to parental anxiety, excluding estimates derived from the sibling-comparison design

The effect estimate for postnatal anxiety exposure in the MoBa was unique in being derived from a sibling comparison design (Gjerde et al., 2018). The sibling-comparison design corrects for all unmeasured covariates shared between siblings in a family. This includes social factors as well

as the parental genome, while the other quasi-experimental designs included in our meta-analysis account only for genetic factors. As such, the MoBa estimate included more controls compared to those from other cohorts, which may have attenuated the parent-offspring correlation to a greater degree. When excluding the MoBa data from the REM of postnatal anxiety exposure, meta-analytic results revealed a significant pooled correlation of *r*=.16 (95% CI .03, .29), compared to *r*=.13 (95% CI .04, .21).

References

Aktar, E., Majdandzic, M., de Vente, W., & Bogels, S. M. (2013). The interplay between expressed parental anxiety and infant behavioural inhibition predicts infant avoidance in a social referencing paradigm. *Journal of Child Psychology and Psychiatry, 54*(2), 144-156. doi:10.1111/j.1469-7610.2012.02601.x

Capron, L. E., Glover, V., Pearson, R. M., Evans, J., O'Connor, T. G., Stein, A., . . . Ramchandani, P. G. (2015). Associations of maternal and paternal antenatal mood with offspring anxiety disorder at age 18 years. *J Affect Disord, 187*, 20-26. doi:10.1016/j.jad.2015.08.012

Gjerde, L. C., Eilertsen, E. M., Eley, T. C., McAdams, T. A., Reichborn-Kjennerud, T., Røysamb, E., & Ystrom, E. (2018). Maternal Perinatal and Concurrent Anxiety and Mental Health Problems in Early Childhood: A Sibling-Comparison Study. *Child Development, 0*(0). doi:10.1111/cdev.13192

Henrichs, J., Schenk, J. J., Schmidt, H. G., Velders, F. P., Hofman, A., Jaddoe, V. W. V., . . . Tiemeier, H. (2009). Maternal pre- and postnatal anxiety and infant temperament. The generation R study. *Infant and Child Development, 18*(6), 556-572. doi:10.1002/icd.639

O'Connor, T. G., Heron, J., Golding, J., Beveridge, M., & Glover, V. (2002). Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. *Br J Psychiatry, 180*, 502-508. doi:10.1192/bjp.180.6.502

O'Connor, T. G., Heron, J., Golding, J., & Glover, V. (2003). Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *J Child Psychol Psychiatry, 44*(7), 1025-1036. doi:10.1111/1469-7610.00187

O'Donnell, K. J., Glover, V., Barker, E. D., & O'Connor, T. G. (2014). The persisting effect of maternal mood in pregnancy on childhood psychopathology. *Dev Psychopathol, 26*(2), 393-403. doi:10.1017/s0954579414000029

Van den Bergh, B. R., & Marcoen, A. (2004). High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds. *Child Dev, 75*(4), 1085-1097. doi:10.1111/j.1467-8624.2004.00727.x

Figure S1. Non-independent effect sizes derived from the Early Growth and Development Study (EGDS) cohort

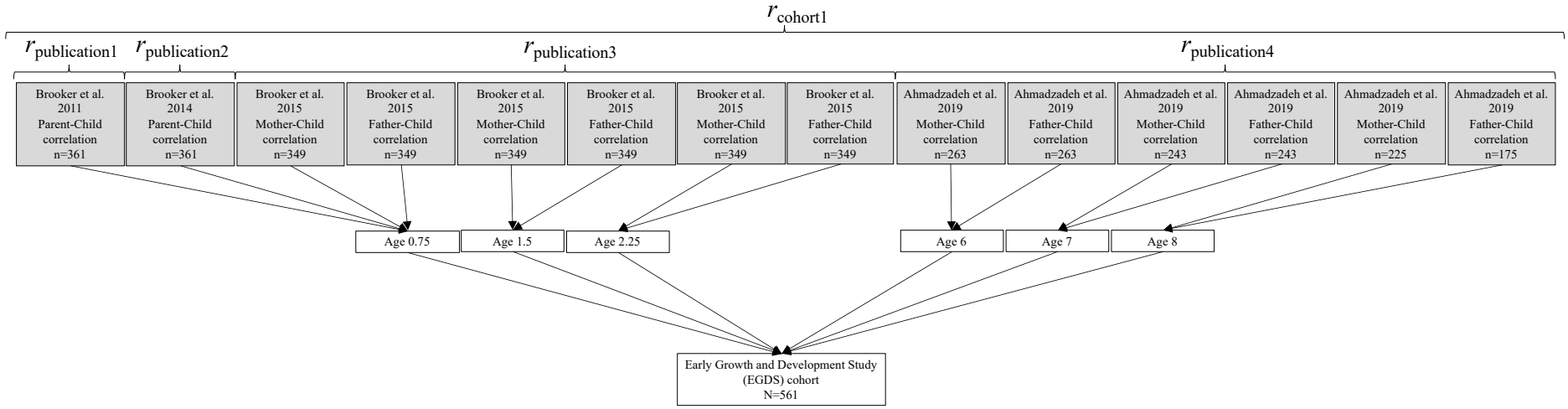
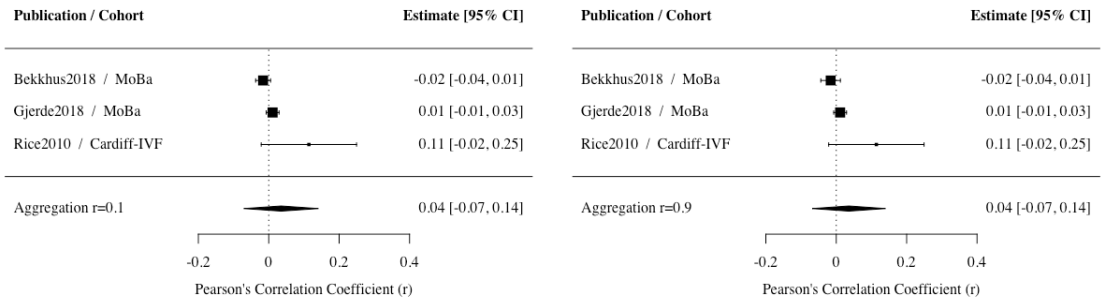


Figure shows the number of effect estimates (grey boxes) extracted from the EGDS adoption cohort. They are non-independent, derived from overlapping individuals and datapoints, nested within a single cohort. The magnitude of the correlation between effect estimates will vary depending on the degree of overlap in the sub-sample, measures and timepoints used. Effect estimates were aggregated within publications to account for their correlation ($r_{publication}$). In a more stringent approach, effect estimates were aggregated within cohorts to account for their correlation (r_{cohort}).

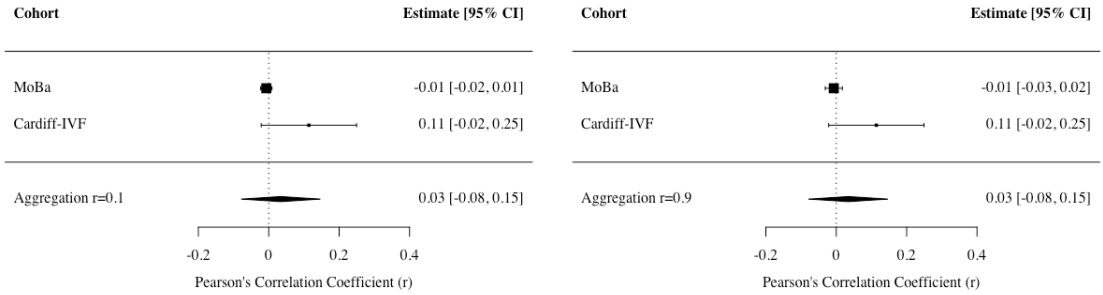
Figure S2. Meta-analytic findings in analyses using *r*=.10 and .90 to aggregate non-independent effects across publications and cohorts

Prenatal Anxiety Exposure

A. Estimates pooled by publication, with multilevel clustering by cohort

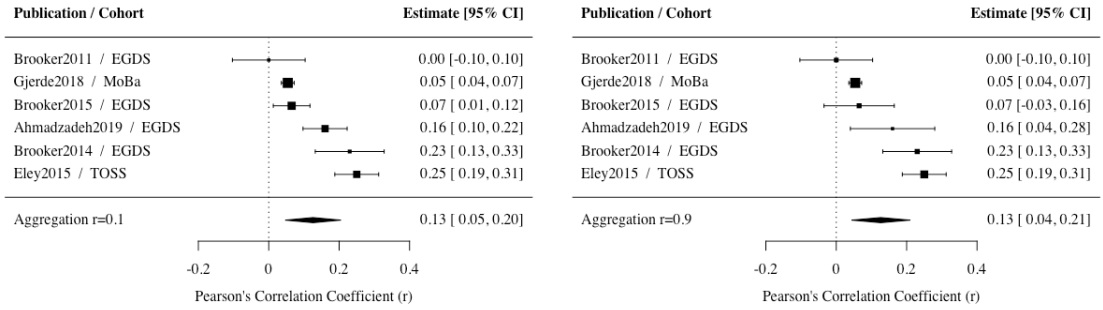


B. Estimates pooled by cohort



Postnatal Anxiety Exposure

A. Estimates pooled by publication, with multilevel clustering by cohort



B. Estimates pooled by cohort

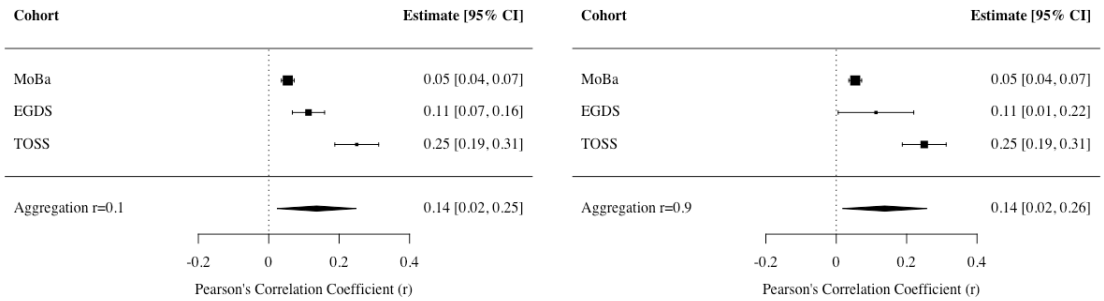
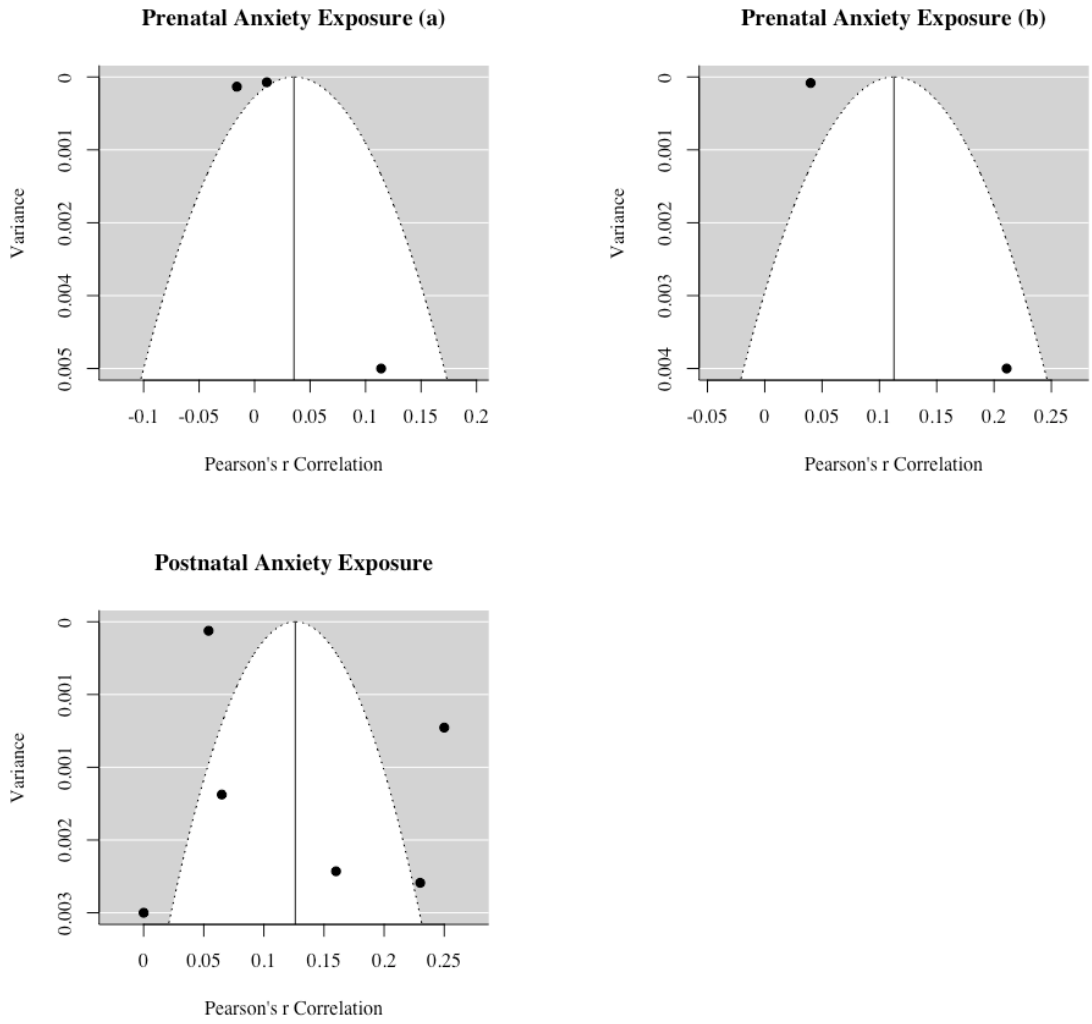


Figure S3. Funnel plots for sampling variance by effect size Pearson's *r*



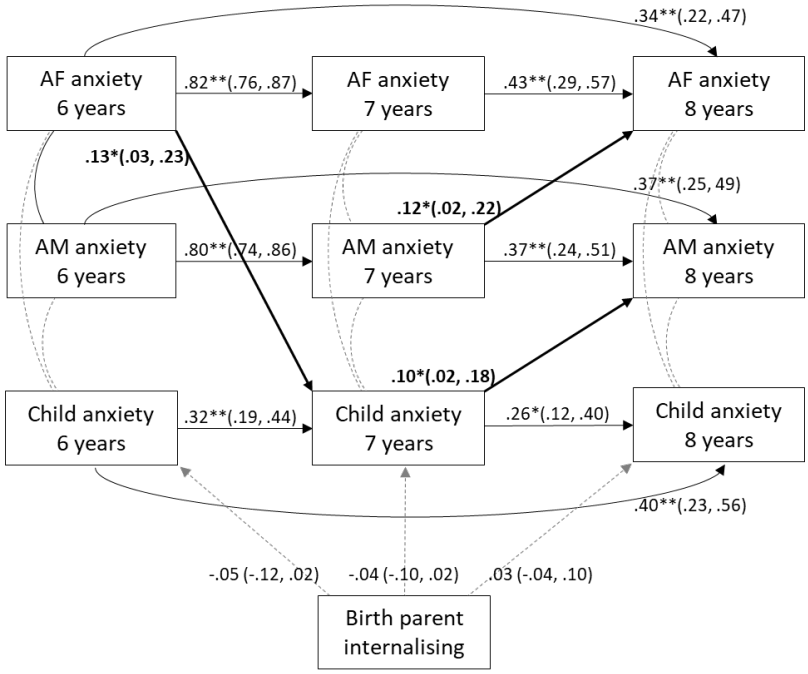
Funnel plots for sampling variance by effect size Pearson's *r* to evaluate publication bias. The vertical solid line represents the pooled effect sizes (Pearson's *r*) from the multilevel random effects models (MREMs). The curved dotted lines show the expected 95% confidence intervals around the summary effect size. A funnel plot that is symmetrical with respect to the pooled effect size (vertical solid line) indicates that the effect size estimates differ between small- and large-sized studies. For prenatal anxiety exposure, a = estimates have been adjusted for postnatal anxiety exposure; b = estimates have not been adjusted for postnatal anxiety exposure. Some evidence for funnel plot asymmetry is suggested for in all panels, although robust conclusions cannot be drawn from so few studies. Egger's regression test was underpowered to detect significant asymmetry.

Appendix B

Supplementary materials for Chapter 3

Figure S1. Results from the first sensitivity analysis, with child anxiety measured using the Eley Anxiety Measure [a]

Figure shows the constrained structural equation model, examining associations between adoptive-father (AF), adoptive-mother (AM) and child anxiety symptoms. Standardised parameter estimates are shown, *p<.05, **p<.001 (95% CI). Composite birth parent internalising data is included as a proxy measure for child inherited anxiety risk. Non-significant cross-lagged paths are dropped, remaining non-significant paths shown in dashed lines. Covariates are not displayed. Mother-child results remained consistent with our primary analyses. A father-to-child path was found, although this did not replicate the primary findings in the paper. Model fit statistics are shown in Table S1.

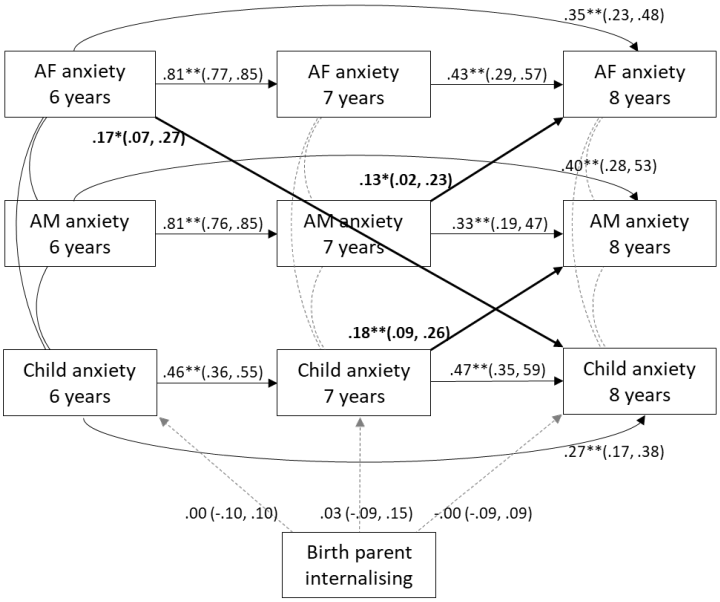


[a] The Eley Anxiety Measure comprises 25 items in 6 subscales that reflect the major anxiety diagnoses and temperamental contribution to anxiety-related behaviours (general distress; separation anxiety; fear; obsessive compulsive behaviours; shy and inhibited behaviors; and poor self-esteem). Previously researchers have shown that items on this scale can distinguish between differing aspects of anxiety-related behaviours in children as young as 4 years (Eley et al., 2003). As with the CBCL, items were assessed via a three-point Likert scale and average mean scores from adoptive mothers and fathers were calculated (mother α=.93-.95, father α=.95-.96; parent report correlations as age 6/7/8 *r*=.26/.17/.29). Descriptive statistics are listed in Table S2.

Figure S2. Results from the second sensitivity analysis, with child anxiety measured using (a) father and (b) mother reports separately on the CBCL Anxious/Depressed subscale.

Figures show the constrained structural equation models, examining associations between adoptive-father (AF), adoptive-mother (AM) and child anxiety symptoms. Standardised parameter estimates are shown *p<.05, **p<.001 (95% CI). Composite birth parent internalising data is included as a proxy measure for child inherited anxiety risk. Non-significant cross-lag paths are dropped, remaining non-significant paths shown in dashed lines. Covariates are not displayed. Mother-child results remained consistent with our primary analyses, but a significant father-to-child effect was only found when using paternal reports of child anxiety symptoms.

(a)



(b)

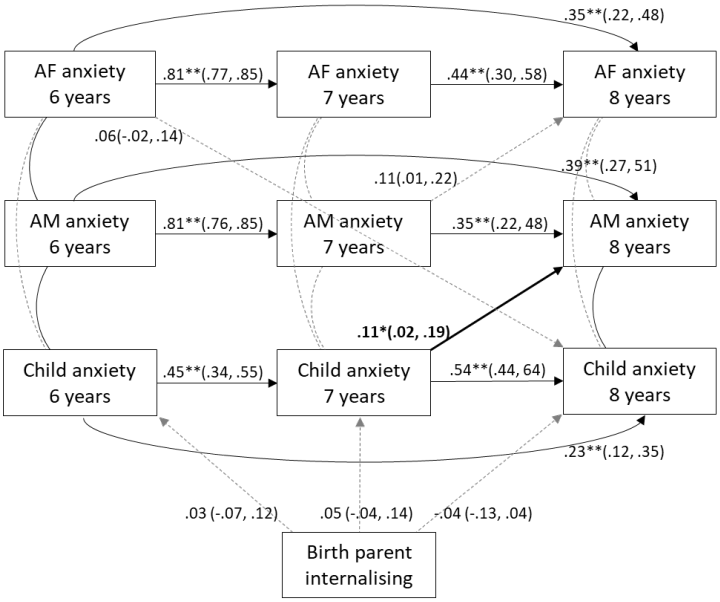


Table S1. Model fit indices for the unconstrained and constrained structural equation models.

All paths were freely estimated in the unconstrained models. All non-significant cross-lag paths were constrained in the final models.

Model	*df*	χ^2	p	RMSEA (95% CI)	CFI	TLI	SCR
Primary analysis							
Child symptoms measured by CBCL Anxious/Depressed subscale							
Unconstrained	73	52.74	0.96	<.001 (.000-.000)	1.00	1.03	1.01
Constrained	88	59.40	0.99	<.001 (.000-.000)	1.00	1.04	1.02
Sensitivity analysis 1							
Child symptoms measured by Eley Anxiety Measure							
Unconstrained	73	51.00	0.98	<.001 (.000-.000)	1.00	1.04	1.00
Constrained	88	57.13	0.10	<.001 (.000-.000)	1.00	1.05	1.01
Sensitivity analysis 2							
Child symptoms measured by CBCL Anxious/Depressed subscale, adoptive father report							
Unconstrained	73	53.81	0.96	<.001 (.000-.000)	1.00	1.03	1.02
Constrained	88	69.30	0.93	<.001 (.000-.010)	1.00	1.03	1.01
Child symptoms measured by CBCL Anxious/Depressed subscale, adoptive mother report							
Unconstrained	73	56.48	0.92	<.001 (.000-.011)	1.00	1.03	1.02
Constrained	88	62.98	0.98	<.001 (.000-.000)	1.00	1.04	1.02

RMSEA (95% CI)= Root-Mean Square Error of Approximation (95% confidence intervals)
CFI = Comparative Fit Index
TLI = Tucker Lewis Index
SCR = Satorra-Bentler Scaling Correction

Table S2. Descriptive statistics for the Eley Anxiety Measure.

Child anxiety did not change significantly over time ($F_{2,451}$=1.56, p=.21) and reports did not differ significantly by sex at any age (*t*(261)=-.67, *p*=.51; *t*(253)=-.59, *p*=.56; *t*(231)=-.65, *p*=.52).

	n	Mean	SD	Min	Max
Child: (measure range 0-8)					
6 years	263	0.92	1.00	0.00	7.83
7 years	255	0.96	1.10	0.00	7.67
8 years	233	1.11	1.28	0.00	8.00

Table S3. Pairwise correlations between adoptive parent and adopted child anxiety symptoms, across four indices of child anxiety symptoms (by measure and parent reporter).

Data transformed and standardised *p<.05, **p<.001.

Adopted Child		Adoptive Mother			Adoptive Father		
		6 years	7 years	8 years	6 years	7 years	8 years
CBCL, Anxious Depressed: Mother report	6 years	**0.19****	**0.17****	0.13	0.00	0.00	0.03
	7 years	0.09	**0.13***	**0.16***	-0.01	-0.02	0.00
	8 years	0.13	**0.17****	**0.26****	0.04	0.02	0.12
CBCL, Anxious Depressed: Father report	6 years	**0.16****	**0.17****	**0.15***	0.11	0.11	0.15
	7 years	0.06	**0.16***	**0.23****	**0.21****	**0.23****	**0.21****
	8 years	0.08	0.05	0.06	**0.27****	**0.21****	**0.29****
Eley Anxiety Measure: Mother report	6 years	**0.15***	0.13	0.11	-0.05	0.00	-0.06
	7 years	0.12	**0.17****	**0.16***	0.03	0.02	0.10
	8 years	0.08	0.11	0.13	-0.03	-0.01	0.01
Eley Anxiety Measure: Father report	6 years	0.10	0.08	**0.16***	**0.23****	**0.20****	**0.28****
	7 years	0.05	0.06	0.13	**0.27****	**0.21****	0.16
	8 years	0.03	0.01	-0.02	**0.17***	0.10	**0.24****

Appendix C

Supplementary materials for Chapter 4

Table S1. Descriptive statistics for measures of parental criticism and offspring internalising symptoms in two samples

Sample	Reporter (N items)	Chronbach's alpha	N	Raw / Log transformed data			
				Mean (SD)	Variance	Skew	Kurtosis
Parental criticism							
Children-of-Twins (TOSS)	Parent (10) [a]	.86	1,721	17.4 (5.26)/2.16 (0.54)	27.7/0.30	0.98/-0.33	3.83/2.85
Adolescent Twins (TCHAD)	Parent (10) [a]	.90	2,112	16.9 (5.89)/0.65 (0.27)	34.7/0.07	1.07/0.51	3.92/2.50
Offspring internalising symptoms							
Children-of-Twins (TOSS)	Parent (30) [b]	.81	1,706	3.83 (4.21)/1.65 (0.61)	17.8/0.37	2.17/0.28	10.5/2.70
	Offspring (30) [c]	.86	1,669	8.70 (6.62)/2.35 (0.55)	43.8/0.30	1.35/-0.57	5.30/4.44
	Composite	--	1,743	6.26 (4.63)/1.81 (0.52)	21.4/0.27	1.50/-0.20	5.87/3.35
Adolescent Twins (TCHAD)	Parent (30) [b]	.80	2,087	3.40 (4.50)/1.60 (0.60)	20.3/0.36	2.55/0.40	11.3/3.14
	Offspring (30) [c]	.88	2,313	8.34 (7.14)/2.33 (0.58)	50.9/0.34	1.35/-0.49	5.02/3.69
	Composite	--	2,420	6.16 (5.48)/2.07 (0.51)	30.0/0.26	1.77/-0.19	7.46/3.39

[a] Expressed Emotion measure. [b] Child Behaviour Checklist. [c] Youth Self-Report.

Table S2. Correlations in monozygotic (MZ) and dizygotic (DZ) families, using self-report for adolescent internalising symptoms

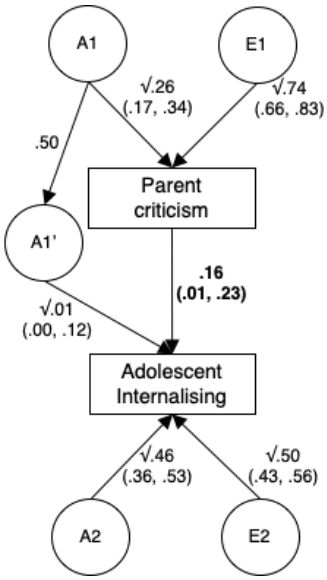
	MZ twin families	DZ twin families
Parental criticism		
Twin correlation [a]	.25	.14
Parental criticism and self-report offspring internalising symptoms		
Parent-child correlation [b]	.18	.18
Avuncular correlation [a]	.07	.04
Self-report offspring internalising symptoms		
Cousin correlation [a]	.13	.07
Twin correlation [c]	.50	.25

[a] From the Children-of-Twins sample, TOSS. [b] From the TOSS and the adolescent twin sample, TCHAD. [c] From the TCHAD.

Table S3. Model fit statistics and comparisons

					Compare to full model			Compare to AE model		
		-2LL	df	AIC	χ^2	Δ df	*p*	χ^2	Δ df	*p*
Models using composite score for adolescent internalising symptoms	Full model (ACE model)	20361	7545	5271	-	-	-	-	-	-
	No C paths (AE model)	20361	7547	5267	.08	2	.96	-	-	-
	AE model with no a1' path	20365	7548	5269	3.9	3	.28	3.8	1	.05
	AE model with no *p* path	20440	7548	5344	79	3	<.001	79	1	<.001
Models using self-report for adolescent internalising symptoms	Full model (ACE model)	20187	7368	5451	-	-	-	-	-	-
	No C paths (AE model)	20187	7370	5447	.11	2	.95	-	-	-
	AE model with no a1' path	20188	7371	5446	.80	3	.85	.69	1	.41
	AE model with no *p* path	20212	7371	5470	24	3	<.001	24	1	<.001

Figure S1. Model results, showing the association between self-reported parental criticism and self-reported adolescent offspring internalising symptoms



A1 = additive genetic effects on parent trait; A2 = additive genetic effects specific to adolescent trait; A1′ = additive genetic effects common to parent and adolescent traits (path from A1 to A1′ is fixed to .50 because offspring inherit 50% of their parent's genes); E1/E2 = nonshared environmental effects on parent/adolescent trait. Variance components are displayed, with the residual intergenerational association in bold (standardised path beta coefficient). The relative contribution of A1' in explaining the phenotypic parent-child correlation is calculated by multiplying the genetic paths connecting each trait, divided by the total phenotypic correlation (r = .18).

Table S4. Exploring statistical power to detect genetic confounding between parental criticism and adolescents' self-reported internalising symptoms (phenotypic correlation = .18)

	Specified/estimated parameters						% rPH attributable to A1'	Power to detect A1' (α = .05)
	E1	A1	E2	A2	A1'	*p*		
Study model	.74/.75	.26/.25	.50/.51	.46/.45	.01/.00	.16/.17	7	.07
Simulated models	.74/.74	.26/.26	.50/.51	.00/.00	.47/.48	.01/.01	94	1.0
	.74/.74	.26/.26	.50/.51	.10/.11	.37/.37	.03/.03	86	1.0
	.74/.74	.26/.26	.50/.51	.20/.21	.27/.27	.05/.05	73	1.0
	.74/.74	.26/.26	.50/.51	.30/.31	.17/.15	.08/.08	56	.93
	.74/.74	.26/.26	.50/.51	.32/.33	.15/.14	.09/.09	51	.88
	.74/.74	**.26/.26**	**.50/.51**	**.34/.35**	**.13/.12**	**.10/.10**	**47**	**.82**
	.74/.74	.26/.26	.50/.51	.35/.36	.12/.10	.10/.10	45	.78

We simulate data for 876 adult twin pairs with one child per twin and 1030 adolescent twin pairs with one parent per pair. Parameters are specified based on supplementary study results, where parental criticism heritability was .26 (A1) and adolescent internalising heritability was .47 (A1'+A2). Each row represents a new model. A1' specification is varied across models to manipulate the percentage of rPh (phenotypic correlation) attributable to genetic confounding. Corresponding changes are made to A2 and *p* specifications, to preserve heritability estimates and rPh in each model. Variance components are shown for latent factors (E1, A1, E2 etc.), whereas *p* is a standardised path coefficient (beta). Bolded text shows the model where 80% power to significantly detect A1' was reached.

Table S5. Standardised parameter estimates (95% CIs) and model fit in nested two-sample reciprocal causation Children-of-Twins models

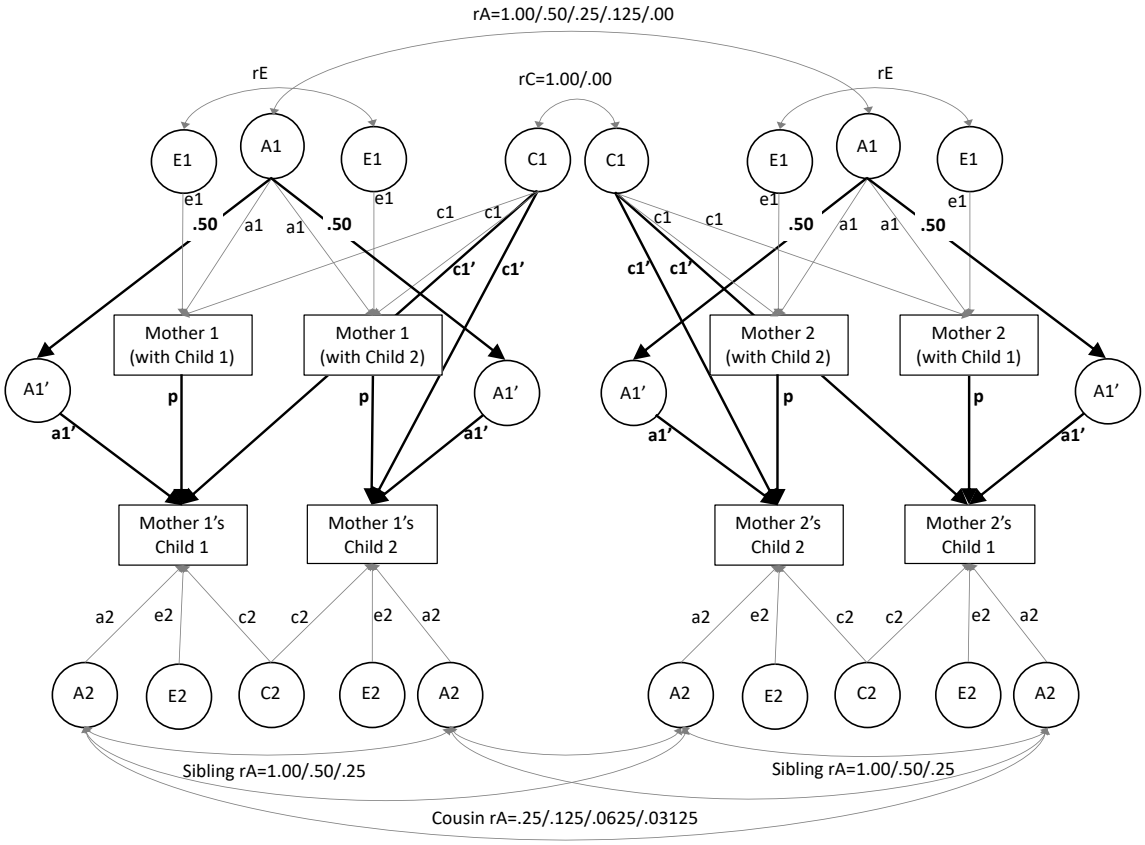
Model	A1	C1	E1	A2	C2	E2	ε	A1'	m	n	-2LL (df)	AIC	χ^2 (Δdf)	p
1	.35 (.18, .46)	-	.29 (.12, .79)	.54 (.11, .65)	.02 (.00, .20)	.04 (.00, .72)	.34 (.00, .45)	.06 (.00, .32)	-.05 (-.34, .62)	.41 (-.45, .56)	20352.90 (7544)	5264.90		
2	.32 (.18, .46)	-	.36 (.13, .79)	.58 (.41, .65)	-	.08 (.00, .72)	.31 (.00, .44)	.03 (.00, .21)	.06 (-.03, .62)	.33 (-.46, .56)	20352.91 (7545)	5262.91	0.01 (1)	.91
3	.27 (.18, .43)	-	.51 (.16, .79)	.55 (.40, .65)	-	.23 (.00, .60)	.22 (.00, .42)	-	.37 (-.15, .52)	.01 (-.38, .56)	20353.05 (7546)	5261.05	0.15 (2)	.93
4	.34 (.25, .43)	-	.33 (.18, .50)	.58 (.43, .65)	-	.06 (00, .18)	.33 (.19, .42)	.04 (.00, .20)	-	.37 (.25, .51)	20352.93 (7546)	5260.93	0.04 (2)	.98
5	.27 (.18, .35)	-	.51 (.39, .67)	.54 (.39, .60)	-	.24 (.16, .36)	.22 (.08, .30)	.00 (.00, .11)	.40 (.24, .53)	-	20353.02 (7546)	5261.02	0.13 (2)	.94
6	.34 (.27, .41)	-	.35 (.22, .73)	.09 (.00, .21)	-	.05 (00, .41)	.32 (.00, .41)	.55 (.42, .67)	-	-	20439.18 (7547)	5345.18	86.3 (3)	<.001
7	.36 (.27, .44)	-	.28 (.15, .41)	.61 (.56, .66)	-	.03 (00, .10)	.36 (.28, .44)	-	-	.46 (.39, .54)	20355.10 (7547)	5261.10	2.05 (1)	.15
8	.27 (.18, .35)	-	.52 (.41, .60)	.55 (.49, .60)	-	.24 (.16, .34)	.21 (.12, .29)	-	.38 (.33, .44)	-	20353.05 (7547)	5259.05	0.00 (1)	.97

A1 = Additive genetic effects on parental phenotype; C1 = shared-environmental effects on parental phenotype; E1 = nonshared environmental effects on parental phenotype; A2 = genetic effects specific to offspring phenotype; C2 = shared-environmental effects on offspring phenotype; E2 = nonshared environmental effects on offspring phenotype; ε = error term; A1' = genetic effects common to parental phenotype and offspring phenotype; m = phenotypic effect of parent on offspring; n = phenotypic effect of child on parent. Model 1 represents the full model, excluding C1 as advised in Narusyte et al. (2008). In subsequent nested models, empty cells (-) indicate that the parameter was dropped from the model. Model fit in Models 2 – 6 are compared to Model 1. Model 7 (A1' and m dropped) and Model 8 (A1' and n dropped) are compared to Model 3 (A1' dropped).

Appendix D

Supplementary materials for Chapter 5

Figure S1. Full MCoTS structural equation model, based around pairs of mothers who are twins, full-siblings, half-siblings, cousins or unrelated sisters-in-law



A1 = additive genetic effects on mother phenotype; C1 = shared environmental effects on mother phenotype; E1 = unique environmental effects on mother phenotype; A2 = additive genetic effects specific to offspring phenotype; C2 = shared environmental effects specific to offspring phenotype; E2 = unique environmental effects specific to offspring phenotype; rA = genetic correlation between relatives; rC = shared environment correlation between relatives; rE = within-mother correlation between E1 for parenting of child 1 and 2. rE is freely estimated to allow for differences in exposure to mother phenotype between siblings born to the same mother. Bold lines show the intergenerational paths used to decompose influence on covariance between parent and child traits: a1' = genetic effects common to mother and offspring phenotype; c1' = extended family shared environment effects; p = residual, phenotypic effect between parent and offspring traits. The pathway between A1 and A1' is fixed to .50 because parents and children share 50% of their genome. Variance = 1 for all latent factors (omitted for simplicity). For A1' this means that residual variance (after accounting for the path between A1 and A1') is .75.

Table S1. Descriptive statistics for raw data measured using the Emotionality, Activity and Shyness Temperament Questionnaire for offspring and the short form of the Hopkins Symptom Checklist for mothers.

	Age	n	Mean	SD	Skew	Kurtosis
Offspring emotionality	1.5	38676	2.73	.76	.10	-.12
	3	31601	2.79	.77	.11	-.10
	5	23354	2.42	.83	.26	-.17
Offspring activity	1.5	38705	4.02	.65	-.49	-.03
	3	31611	3.62	.70	-.12	-.27
	5	23354	3.22	.71	.21	-.12
Offspring shyness	1.5	38679	2.05	.64	.44	.22
	3	31600	2.22	.68	.40	.17
	5	23335	2.09	.71	.43	.01
Offspring sociability	1.5	38719	3.95	.56	-.07	.16
	3	31601	3.68	.57	-.03	.09
	5	23353	4.07	.63	-.24	-.24
Mother internalising	1.5	37814	1.27	.36	2.38	8.15
	3	30617	1.26	.38	2.50	8.50
	5	23075	1.21	.33	2.79	10.82

Offspring phenotype range = 1 – 5. Mother phenotype range = 1 – 4.

Table S2. Phenotypic, cross-sectional correlations between mothers' internalising symptoms and offspring temperament traits during early childhood

	Mother Internalising		
Child Temperament	1.5 years	3 years	5 years
Emotionality	.15*	.15*	.18*
Activity Level	-.01	-.01	.02
Shyness	.03*	.04*	.05*
Sociability	-.02	-.03*	-.04*

*p<.001, using Bonferroni correction to adjust for multiple tests

Table S3. Goodness of fit tests and parameter estimates for the autoregressive growth curve model (Model 1) fit to within-generation offspring sociability data: fixing variance in the latent slope factor to zero. *Note that this is a different approach to dropping the slope latent factor completely, which would involve removing slope variance, slope mean and covariance between slope and intercept. Here we remove slope variance only.*

A. Chi square goodness of fit tests

	df	**AIC**	**BIC**	**Chi²**	**ΔChi²**	**Δdf**	**p**
Model 1	2	257925.3	257985.9	143.009	--	--	--
Model 1, S variance = 0	3	257926.9	257978.8	146.582	2.568	1	.109

B. Parameter estimates

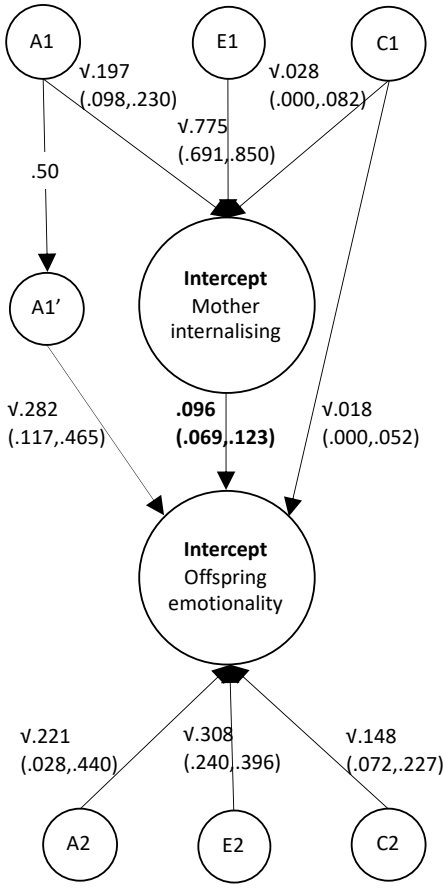
	Variance in baseline stability: I	Variance in rate of linear change: S	Correlation (*r*): I – S	Autoregressive effects: β	Residual error: e
Model 1	.279 (.245, .313)	.005 (-.000, .009)	-.013 (-.019, -.006)	.112 (.085, .140)	.697 (.670, .724)
Model 1, S variance = 0	.249 (.232, .267)	.000 (.000, .000)	-.007 (-.010, -.004)	.133 (.115, .152)	.721 (.707, .735)

Table S4. Chi square goodness of fit tests for nested models in longitudinal analyses of phenotypic, cross-generation data: dropping intergenerational latent factor correlations

Model	**df**	**AIC**	**BIC**	**Chi²**	**ΔChi²**	**Δdf**	**p**
Base model							
Emotionality	9	492385.6	492541.5	87.994	--	--	--
Activity	9	490236.8	490392.6	169.175	--	--	--
Shyness	9	491797.5	491953.4	252.895	--	--	--
Sociability	9	499453.5	499609.4	175.987	--	--	--
Drop correlation between Child Intercept – Mother Intercept							
Emotionality	10	493304.8	493452.0	1009.152	783.237	1	<.0001
Activity	10	490244.5	490391.7	178.912	8.524	1	.0035
Shyness	10	491839.7	491986.9	297.100	38.561	1	<.0001
Sociability	10	499462.4	499609.6	186.890	9.722	1	.0018
Drop correlation between Child Slope – Mother Slope							
Emotionality	10	492504.3	492651.5	208.686	126.884	1	<.0001
Activity	10	490235.0	490382.2	169.381	.197	1	.6569
Shyness	10	491805.7	491952.9	263.118	9.060	1	.0026
Sociability	10	499453.4	499600.6	177.886	1.708	1	.1912
Drop correlation between Child Intercept – Mother Slope							
Emotionality	10	492461.4	492608.6	165.765	59.475	1	<.0001
Activity	10	490238.8	490386.0	173.160	3.721	1	.0537
Shyness	10	491800.1	491947.3	257.485	4.343	1	.0372
Sociability	10	499451.5	499598.7	175.992	.004	1	.9466
Drop correlation between Child Slope – Mother Intercept							
Emotionality	10	492387.8	492534.9	92.111	3.55	1	.0594
Activity	10	490246.7	490393.9	181.106	11.055	1	.0009
Shyness	10	491796.1	491943.3	253.507	.532	1	.4656
Sociability	10	499453.5	499600.7	177.932	1.722	1	.1895

Significance level = .0125 when using Bonferroni correction to account for four multiple tests

Figure S2. Base model results from MCoTS biometric analyses, decomposing the association between baseline stability in mothers' internalising symptoms and baseline stability in offspring emotionality



A1 = additive genetic effects on mother trait; A2 = additive genetic effects specific to offspring trait; A1′ = additive genetic effects common to mother and offspring traits (path from A1 to A1′ is fixed to .50 because offspring inherit 50% of their mother's genes); C1/C2 = common environment effects on mother/offspring trait; E1/E2 = unique environment effects on mother/offspring trait. Path linking C1 to offspring trait represents extended family shared environment effects (c1'). Variance components are displayed in non-bold text. The residual intergenerational association is displayed as a standardised path beta coefficient in bold text. Figure represents a partial path diagram, see Figure S1 for full model specification.

Table S5. Model fit statistics and comparisons for MCoTS models decomposing the association between baseline stability in mothers' internalising symptoms and baseline stability in offspring emotionality

					Compare to 1			Compare to 2		
		-2LL	df	AIC	∆-2LL	∆df	p	∆-2LL	∆df	p
1	Base model	130148.0	85158	-40168.03	--	--	--	--	--	--
2	**Drop C1 c1'**	**130151.6**	**85160**	**-40168.38**	**3.649**	**2**	**.1613**	**--**	**--**	**--**
3	Drop C1 c1' a1'	130192.6	85161	-40129.35	44.678	3	<.0001	41.029	1	<.0001
4	Drop C1 c1' p	130200.6	85161	-40121.39	52.638	3	<.0001	48.989	1	<.0001

Best fitting model is indicated in bold.